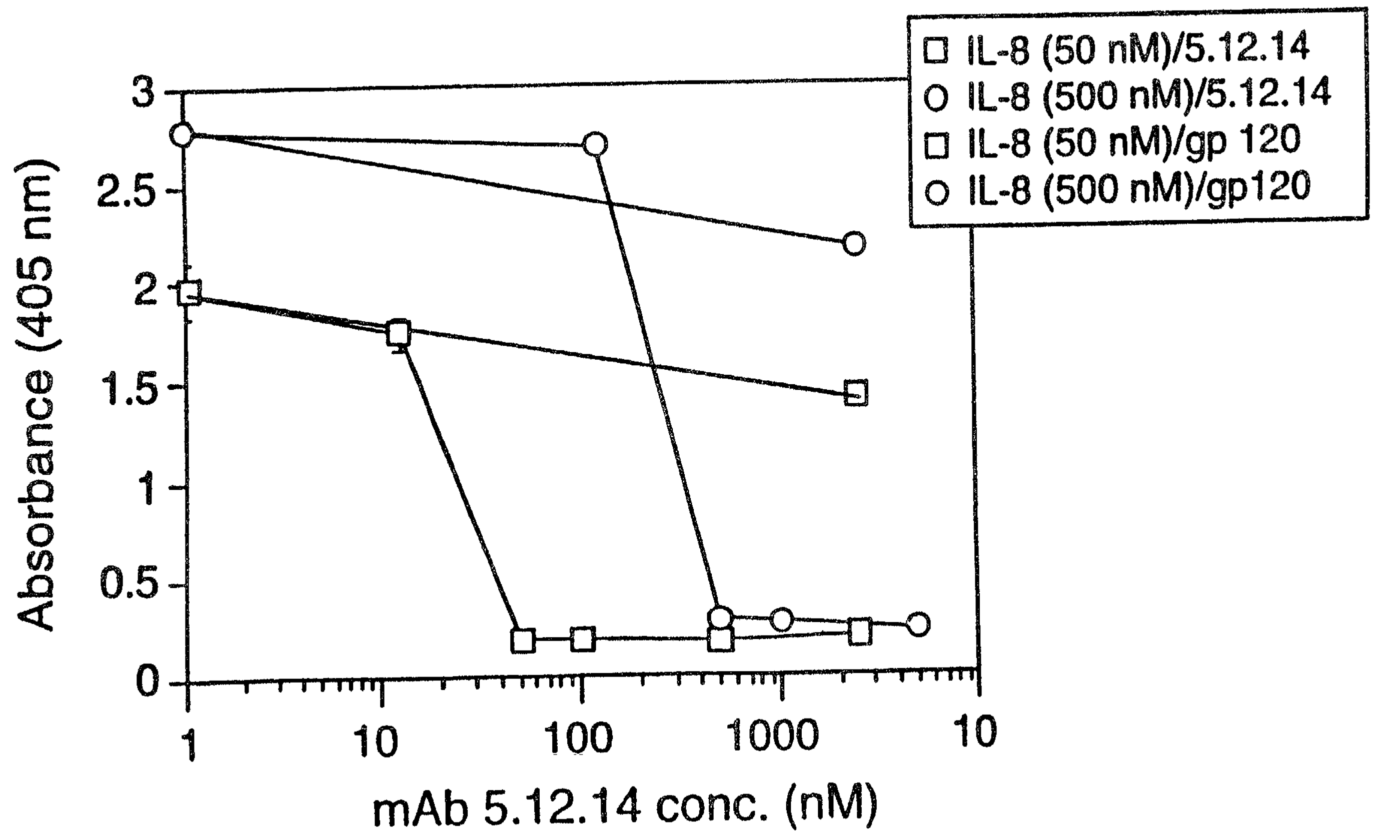
FIG. 1


IL-8 (50 nM)/5.12.14
IL-8 (500 nM)/5.12.14
IL-8 (50 nM)/gp 120
IL-8 (500 nM)/gp120
Absorbance (405 nm)
3
2.5
2
1.5
1
0.5
0
1
10
100
1000
10
mAb 5.12.14 conc. (nM)

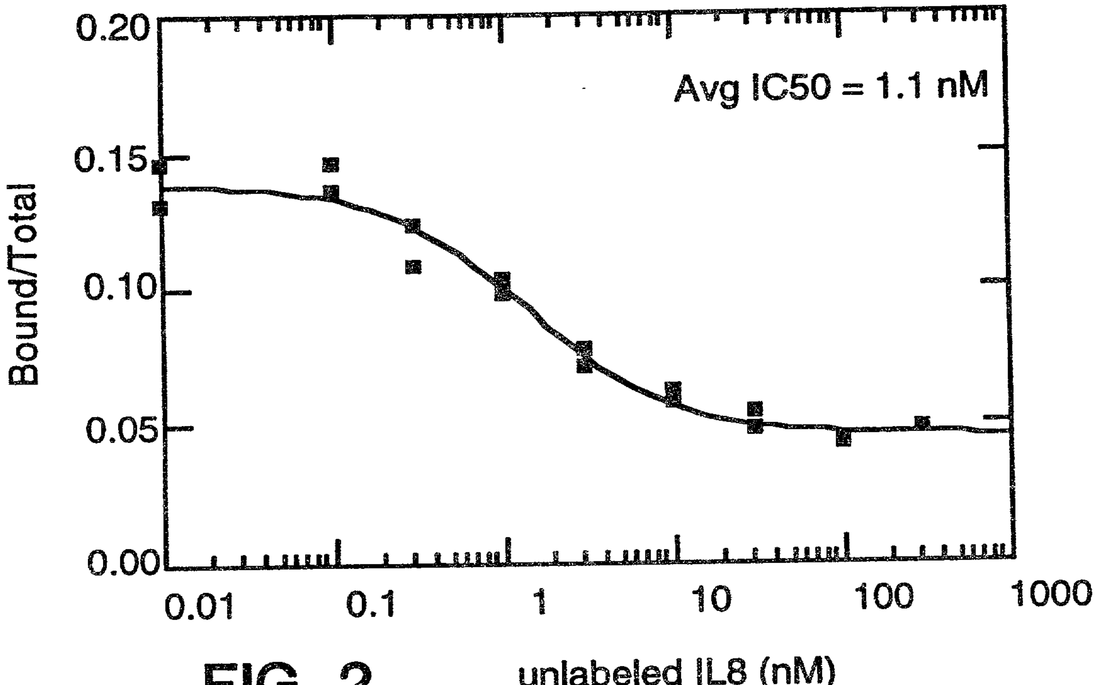

Avg IC50 = 1.1 nM
Bound/Total
0.20
0.15
0.10
0.05
0.00
0.01
0.1
1
10
100
1000
unlabeled IL8 (nM)

FIG. 2

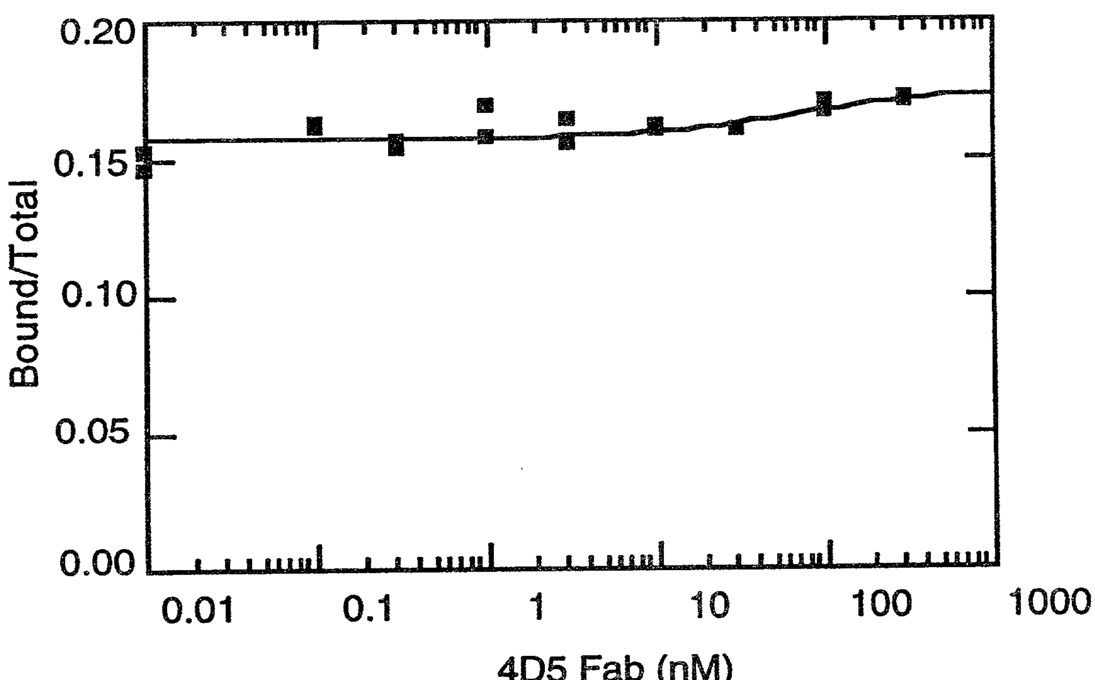

Bound/Total
0.20
0.15
0.10
0.05
0.00
0.01
0.1
1
10
100
1000
4D5 Fab (nM)

FIG. 3

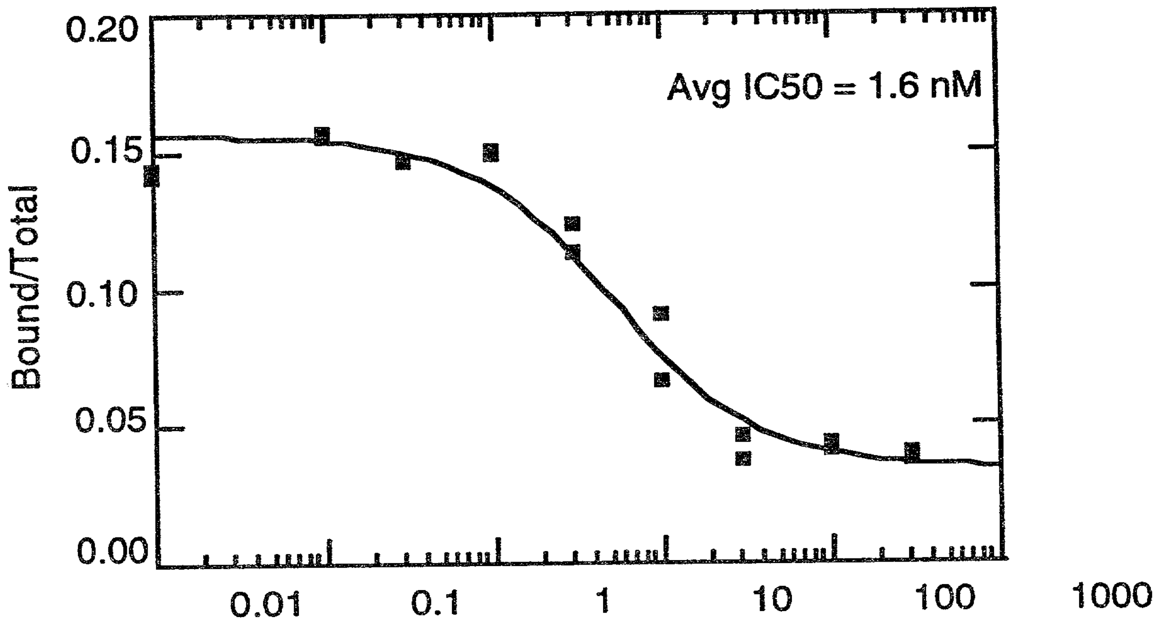

Avg IC50 = 1.6 nM
Bound/Total
0.20
0.15
0.10
0.05
0.00
0.01
0.1
1
10
100
1000
A51214 Fab (nM)

FIG. 4

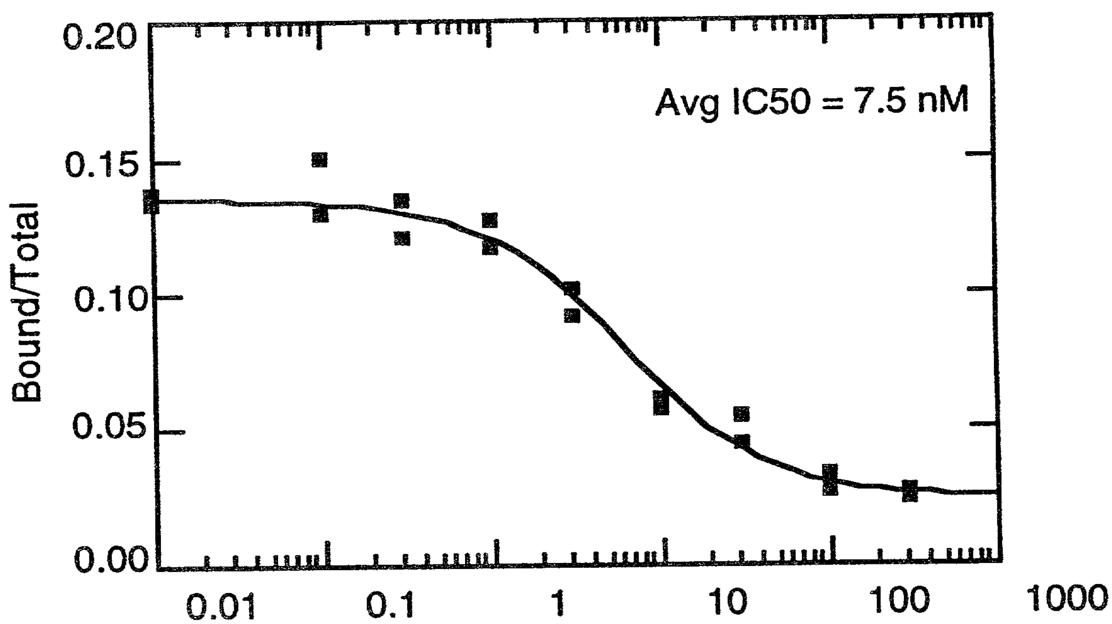

Avg IC50 = 7.5 nM
Bound/Total
0.20
0.15
0.10
0.05
0.00
0.01
0.1
1
10
100
1000
6G425 Fab (nM)

FIG. 5

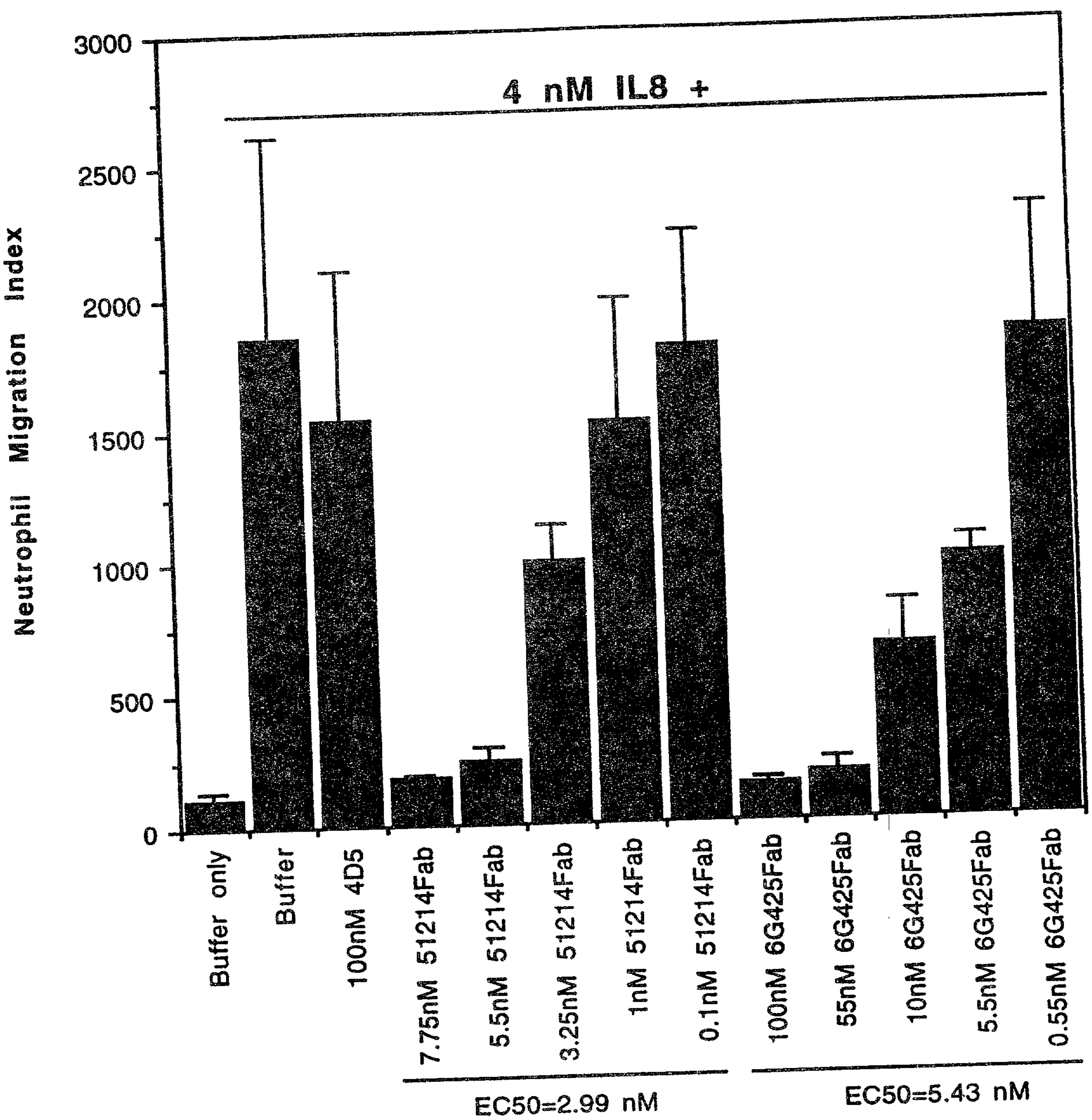
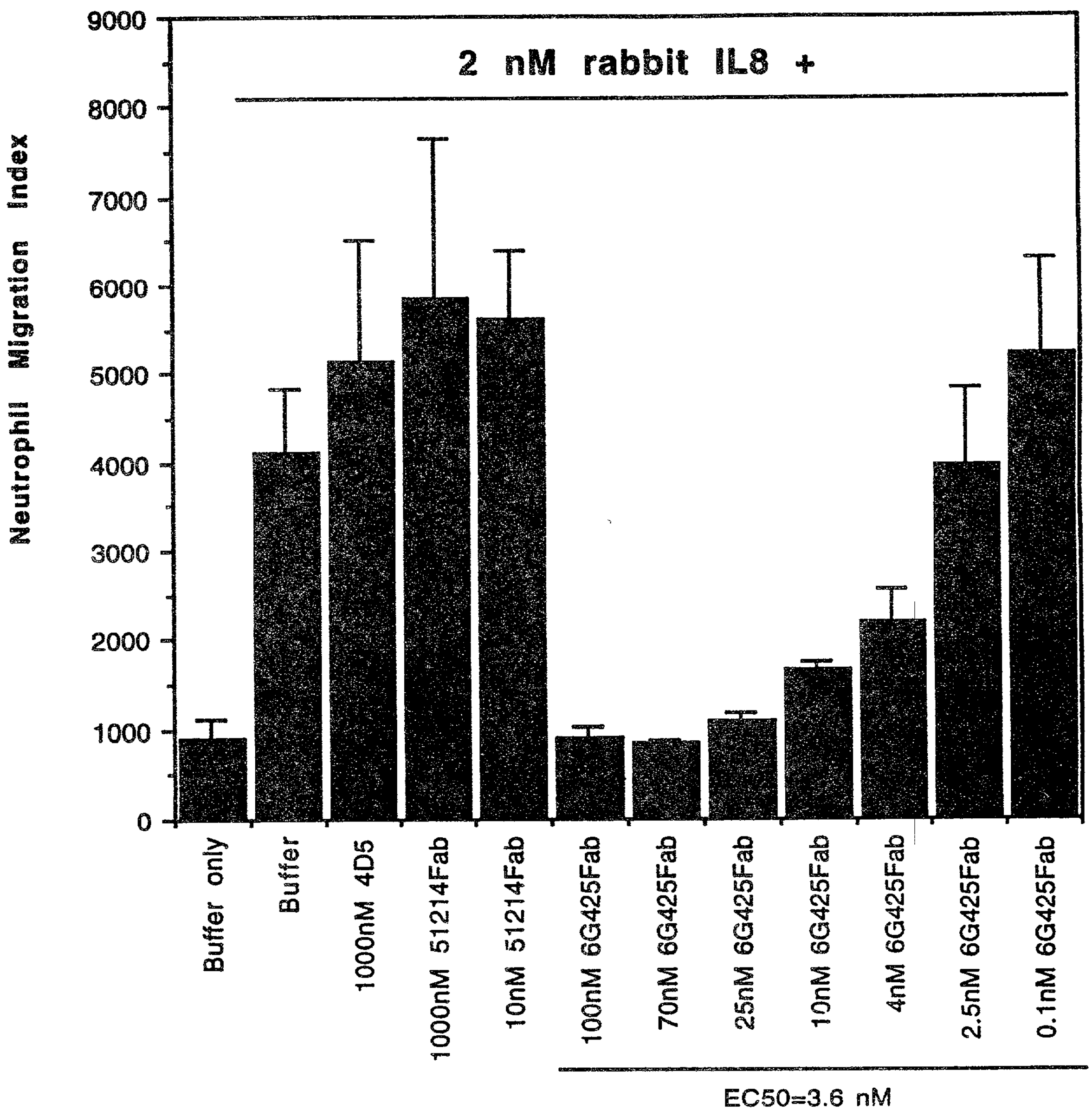

4 nM IL8 +
Neutrophil Migration Index
3000
2500
2000
1500
1000
500
0
Buffer only
Buffer
100nM 4D5
7.75nM 51214Fab
5.5nM 51214Fab
3.25nM 51214Fab
1nM 51214Fab
0.1nM 51214Fab
100nM 6G425Fab
55nM 6G425Fab
10nM 6G425Fab
5.5nM 6G425Fab
0.55nM 6G425Fab
EC50=2.99 nM
EC50=5.43 nM

FIG. 6



2 nM rabbit IL8 +
Neutrophil Migration Index
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
Buffer only
Buffer
1000nM 4D5
1000nM 51214Fab
10nM 51214Fab
100nM 6G425Fab
70nM 6G425Fab
25nM 6G425Fab
10nM 6G425Fab
4nM 6G425Fab
2.5nM 6G425Fab
0.1nM 6G425Fab
EC50=3.6 nM

FIG. 7

FIG. 8

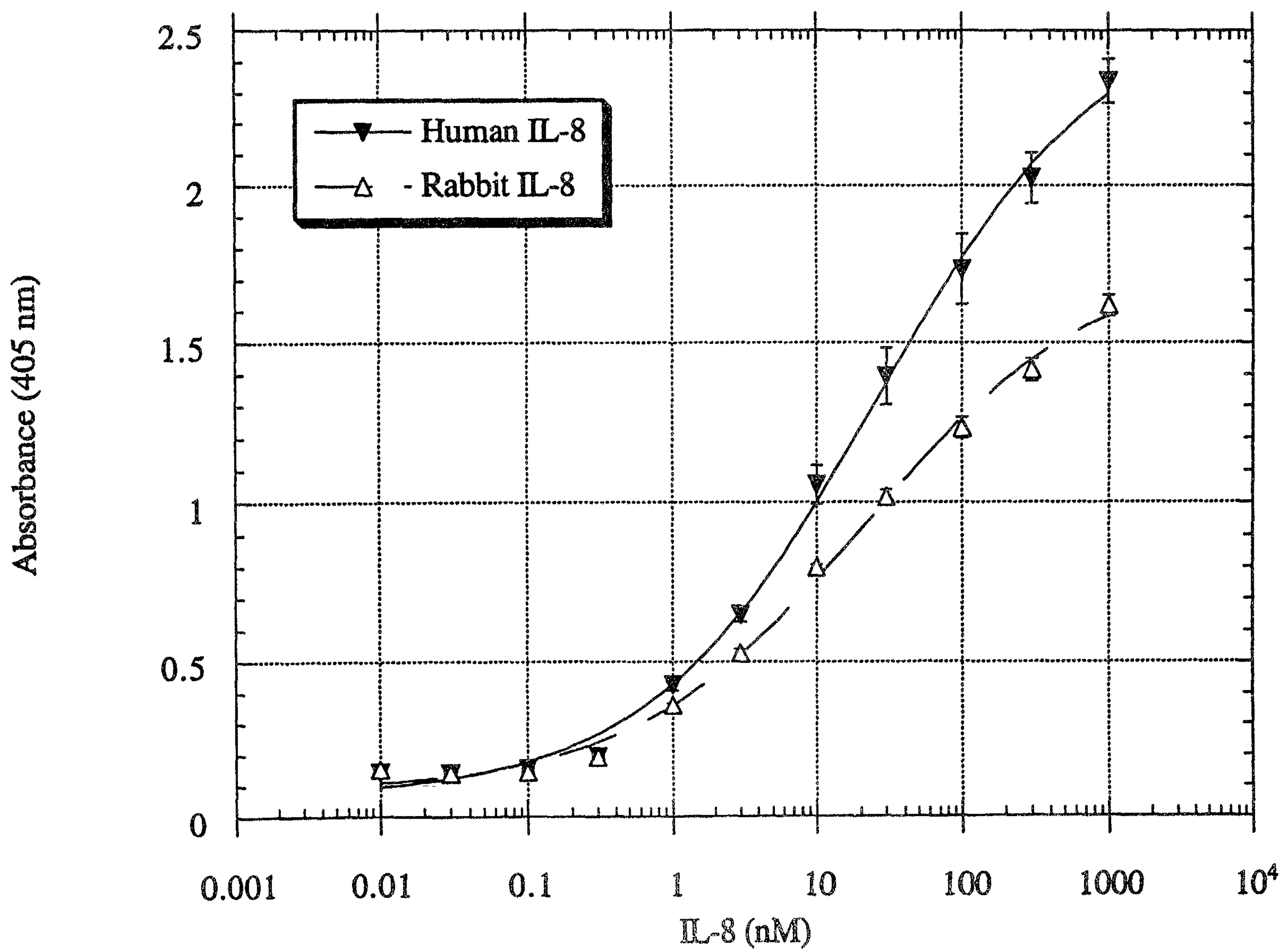
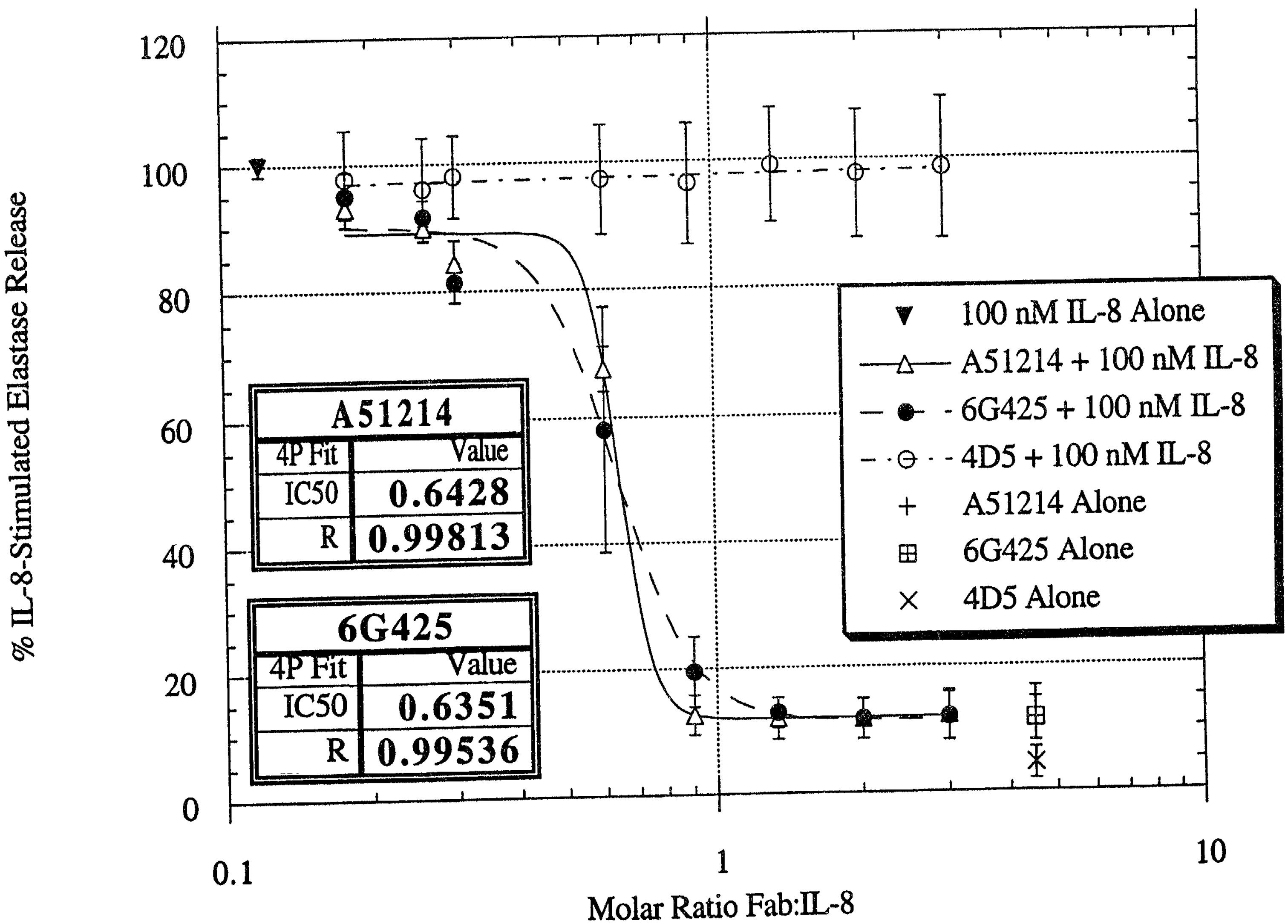
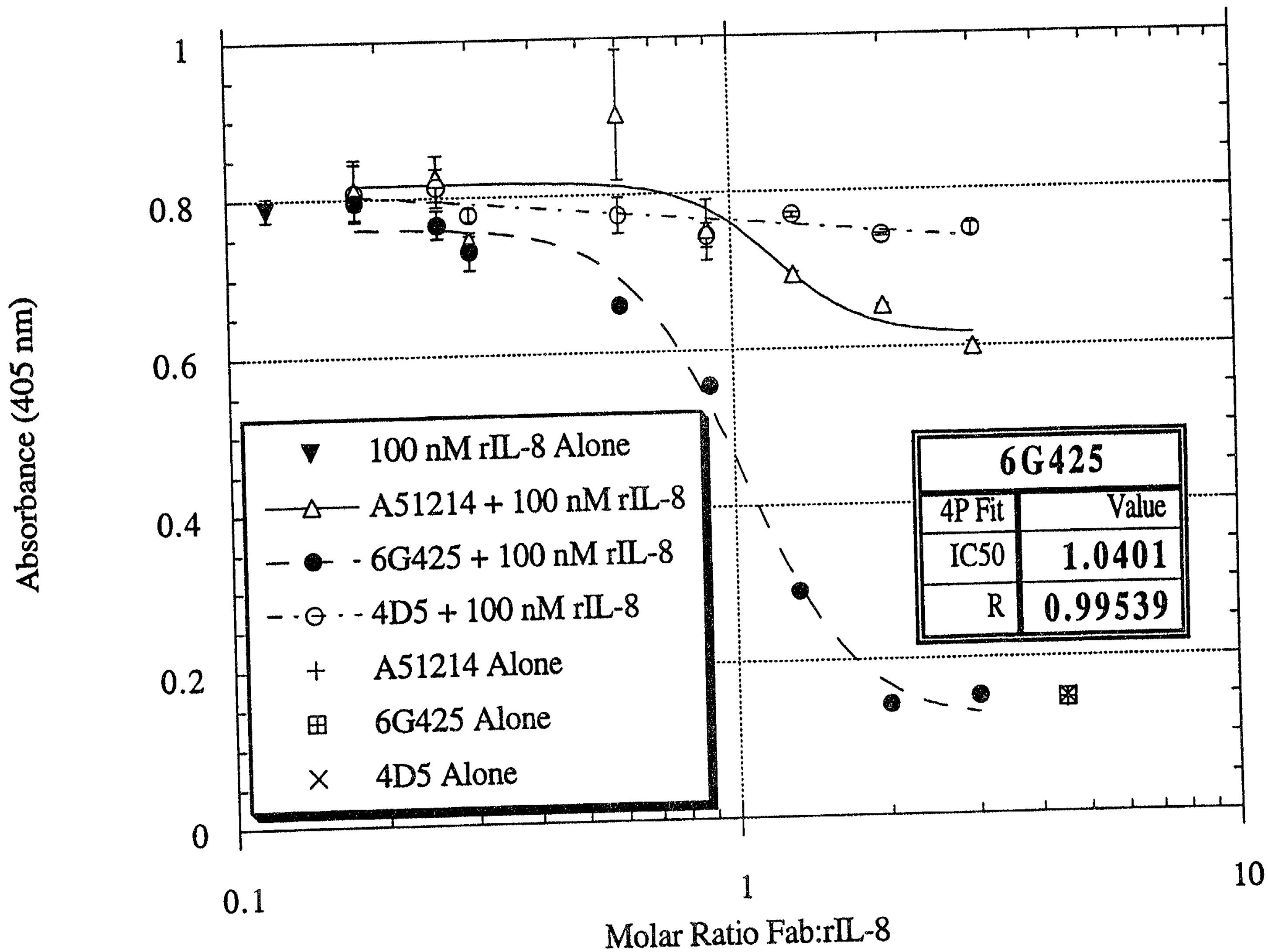

Human IL-8
- Rabbit IL-8
Absorbance (405 nm)
2.5
2
1.5
1
0.5
0
0.001
0.01
0.1
1
10
100
1000
10^4
IL-8 (nM)

FIG. 9



120
100
80
60
40
20
0
% IL-8-Stimulated Elastase Release
0.1
1
10
Molar Ratio Fab:IL-8
100 nM IL-8 Alone
A51214 + 100 nM IL-8
6G425 + 100 nM IL-8
4D5 + 100 nM IL-8
A51214 Alone
6G425 Alone
4D5 Alone
A51214
4P Fit
Value
IC50
0.6428
R
0.99813
6G425
4P Fit
Value
IC50
0.6351
R
0.99536

FIG. 10


1
0.8
0.6
0.4
0.2
0
Absorbance (405 nm)
0.1
1
10
Molar Ratio Fab:rIL-8
100 nM rIL-8 Alone
A51214 + 100 nM rIL-8
6G425 + 100 nM rIL-8
4D5 + 100 nM rIL-8
A51214 Alone
6G425 Alone
4D5 Alone
6G425
4P Fit
Value
IC50
1.0401
R
0.99539

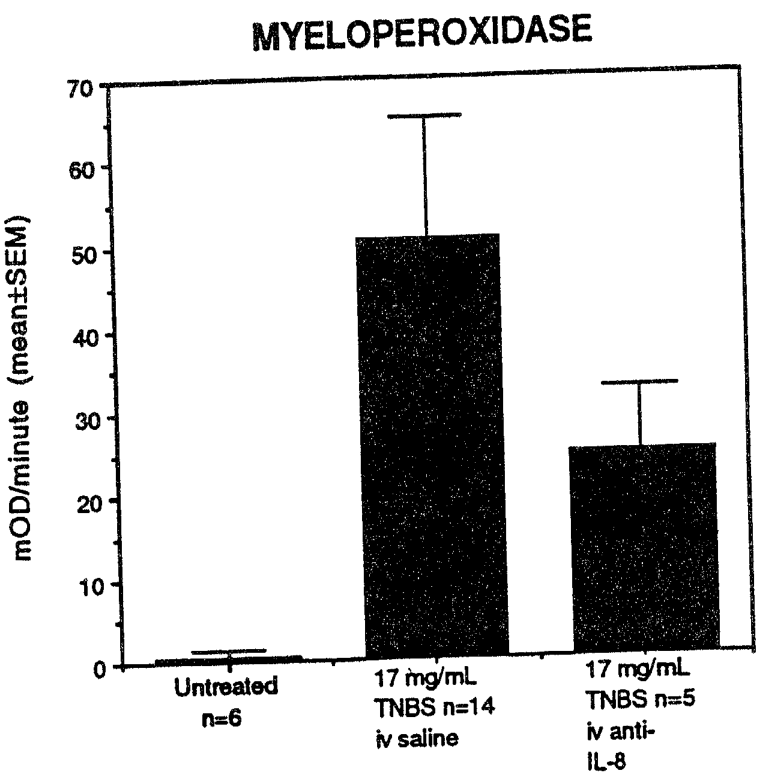


FIG. 11A

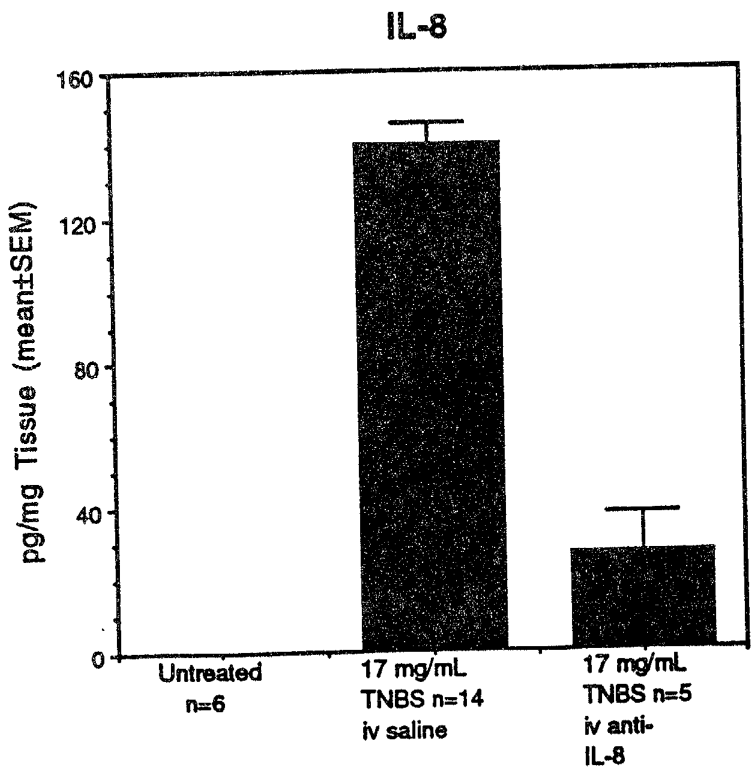


FIG. 11B

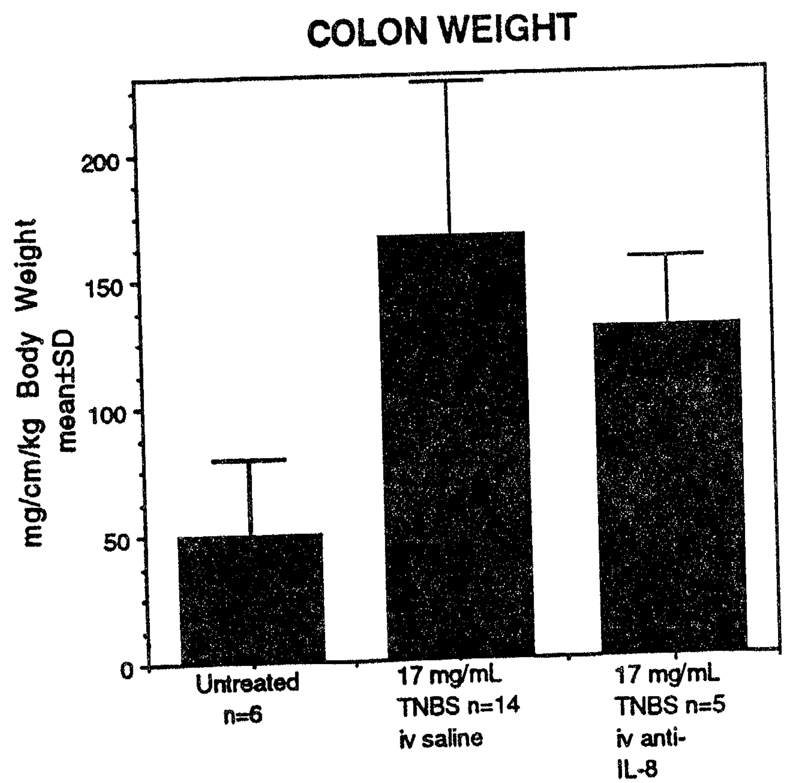


FIG. 11C

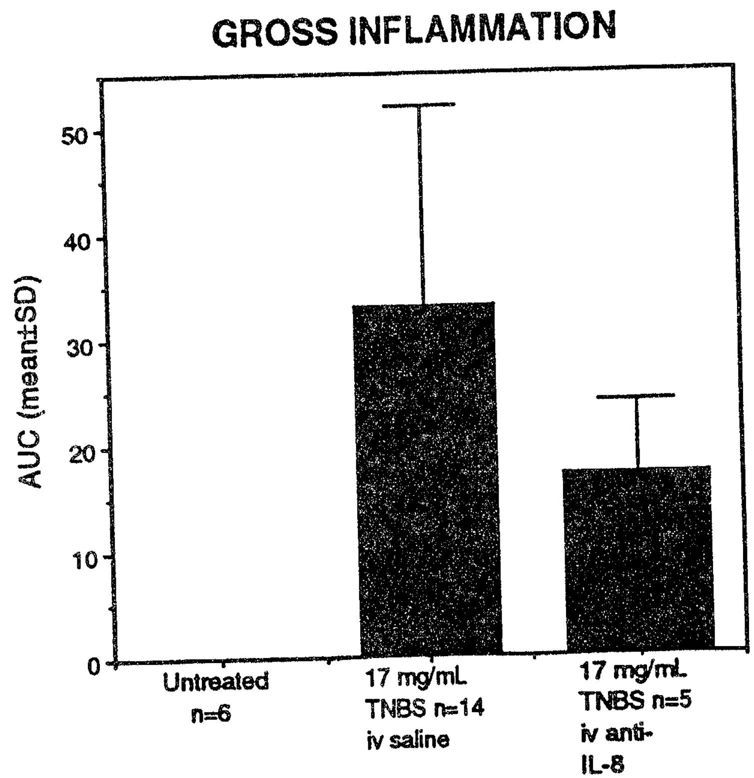


FIG. 11D

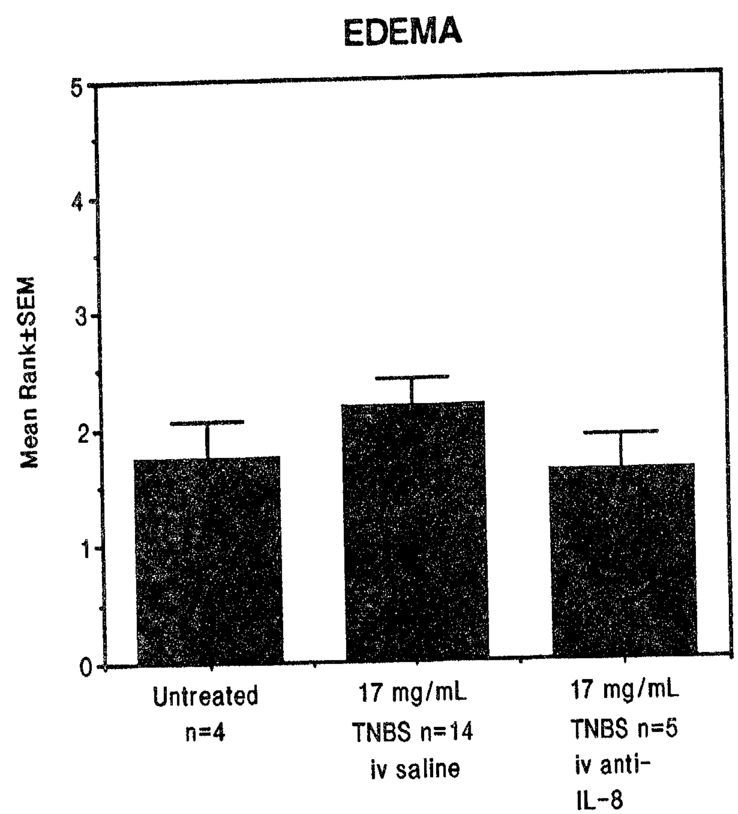


FIG. 11E

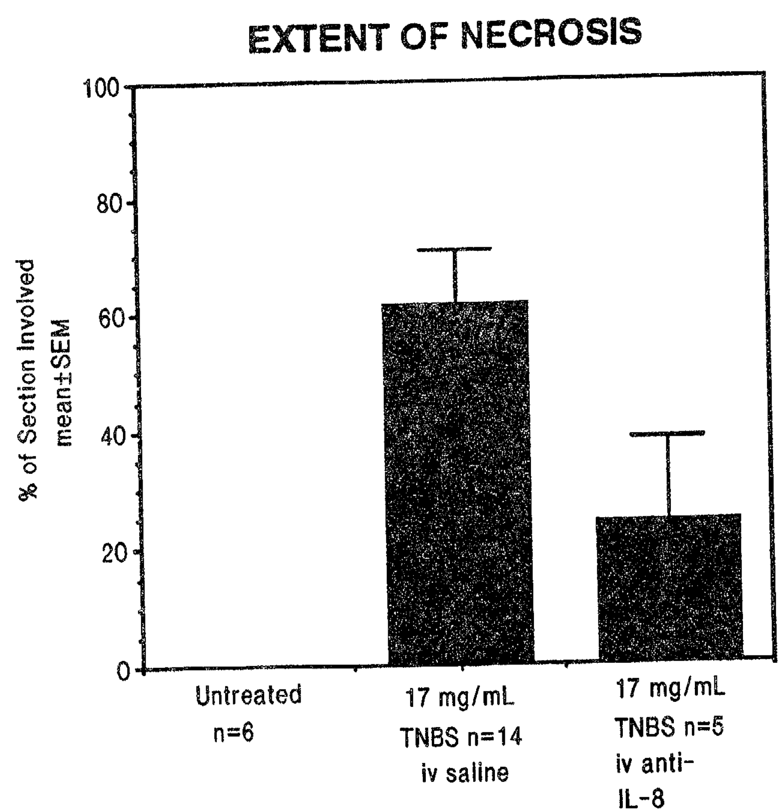


FIG. 11F

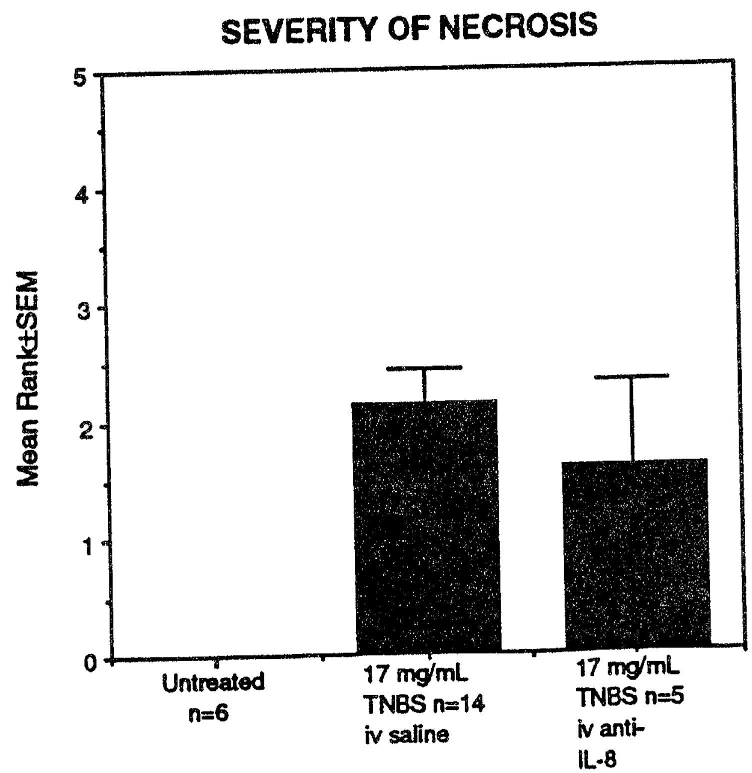


FIG. 11G

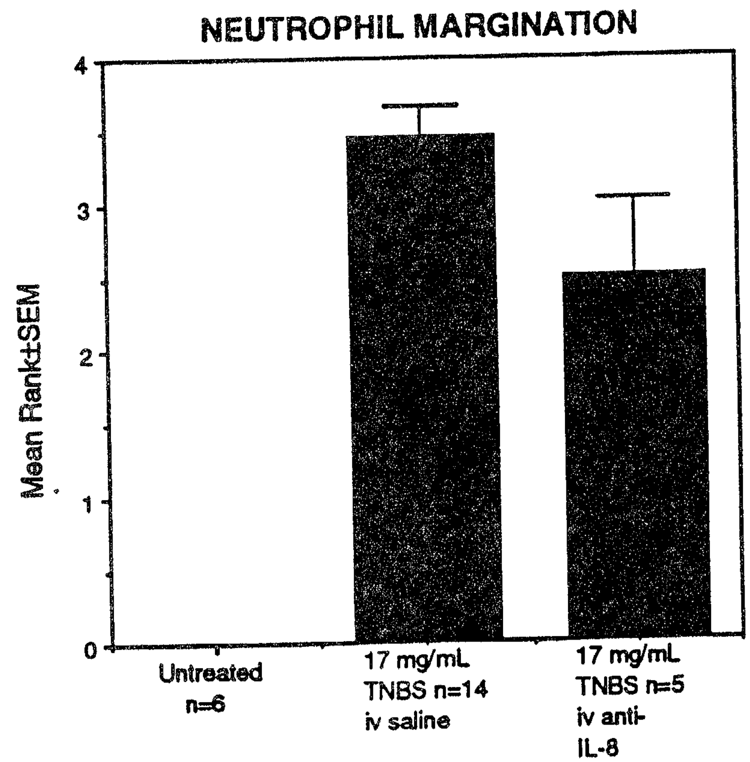


FIG. 11H

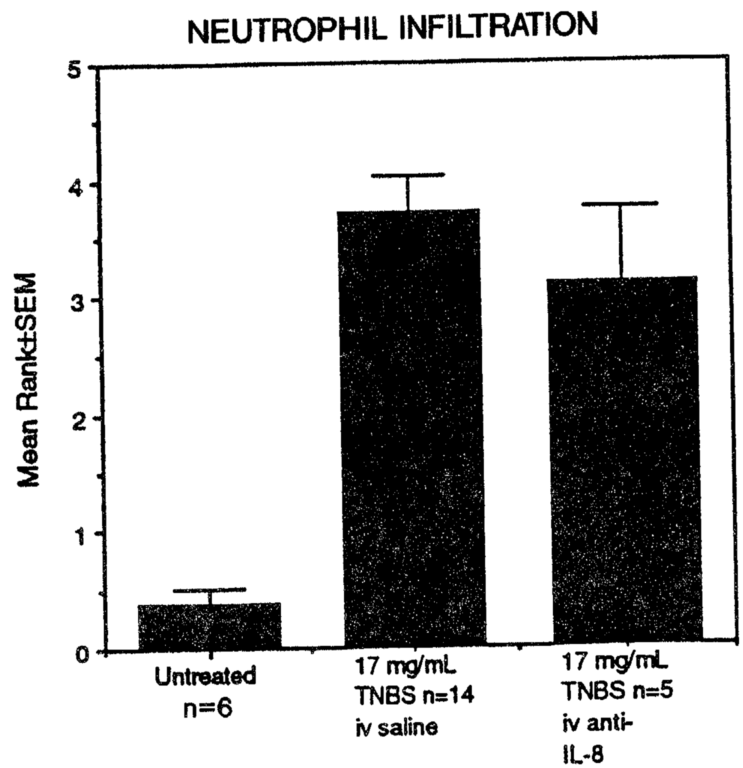


FIG. 11I

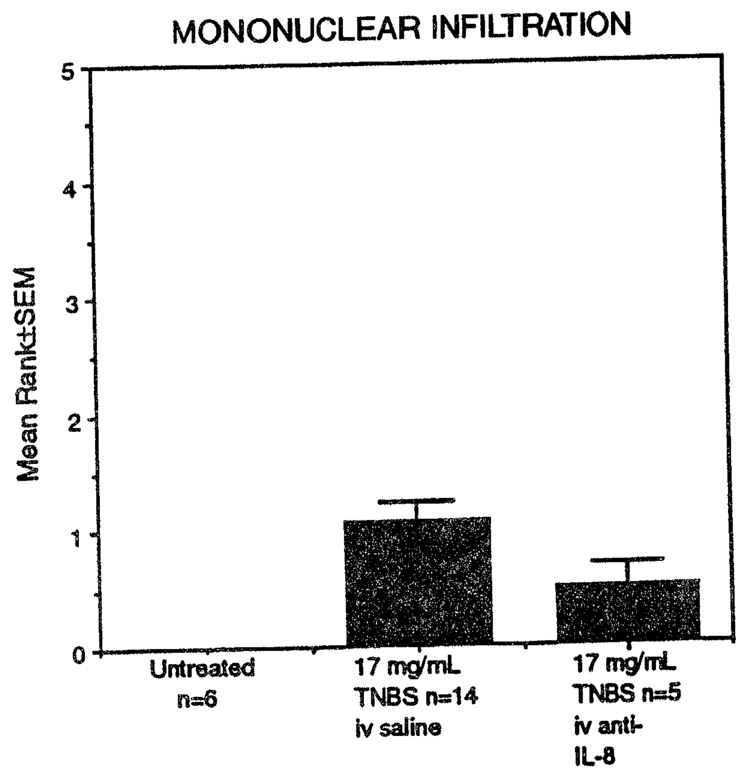
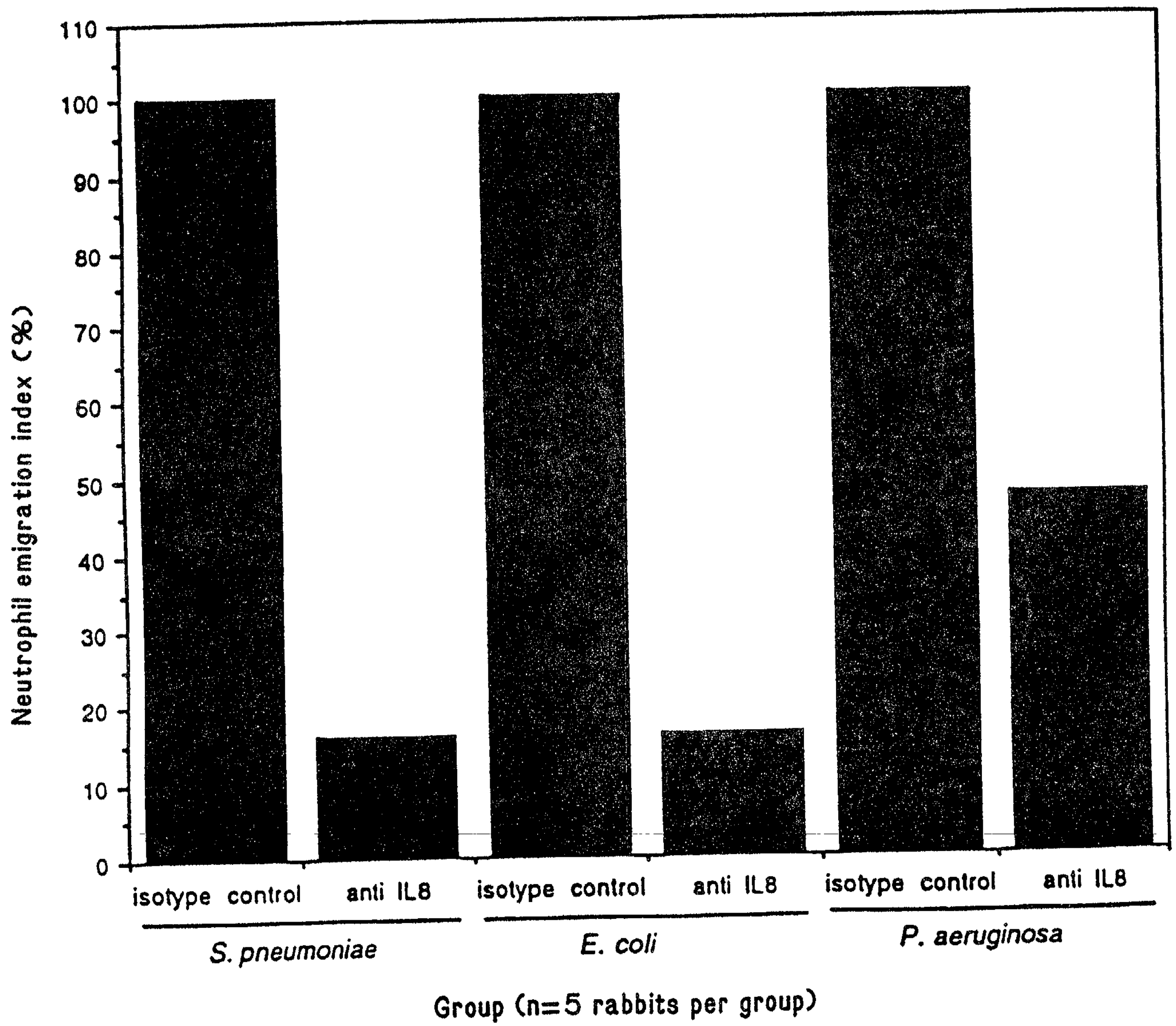


FIG. 11J

FIG. 12


110
100
90
80
70
60
50
40
30
20
10
0
Neutrophil emigration index (%)
isotype control
anti IL8
isotype control
anti IL8
isotype control
anti IL8
S. pneumoniae
E. coli
P. aeruginosa
Group (n=5 rabbits per group)

Light Chain Primers:

FIG. 13

MKLC-1, 22mer

5' CAGTCCAACTGTTCAGGACGCC 3' (SEQ ID NO.1)

MKLC-2, 22mer

5' GTGCTGCTCATGCTGTAGGTGC 3' (SEQ ID NO.2)

MKLC-3, 23mer

5' GAAGTTGATGTCTTGTGAGTGGC 3' (SEQ ID NO.3)

Heavy Chain Primers:

IGG2AC-1, 24mer

5' GCATCCTAGAGTCACCGAGGAGCC 3' (SEQ ID NO.4)

IGG2AC-2, 22mer

5' CACTGGCTCAGGGAAATAACCC 3' (SEQ ID NO.5)

IGG2AC-3, 22mer

5' GGAGAGCTGGGAAGGTGTGCAC 3' (SEQ ID NO.6)

FIG. 14

Light chain forward primer

SL001A-2 35 mer

```
5' ACAAACGCGTACGCT GACATCGTCATGACCCAGTC 3'(SEQ ID NO.7)
                     T  T        T            (SEQ ID NO.8)
                                 A            (SEQ ID NO.9)
```

Light chain reverse primer

SL001B 37 mer

5' GCTCTTCGAATG GTGGGAAGATGGATACAGTTGGTGC 3'(SEQ ID NO.10)

FIG. 15

Heavy chain forward primer

SL002B 39 mer

```
5' CGATGGGCCCGG ATAGACCGATGGGGCTGTTGTTTTGGC 3' (SEQ ID NO.11)
                      T             C           (SEQ ID NO.12)
                      G                         (SEQ ID NO.13)
                      A                         (SEQ ID NO.14)
```

Heavy chain reverse primer

SL002B 39-MER

```
5' CGATGGGCCCGG ATAGACCGATGGGGCTGTTGTTTTGGC 3' (SEQ ID NO.11)
                                                (SEQ ID NO.15)
                      T                         (SEQ ID NO.14)
                      A                         (SEQ ID NO.13)
                      G
```

```
  1 GACATTGTCA TGACACAGTC TCAAAAATTC ATGTCCACAT CAGTAGGAGA CAGGGTCAGC
    CTGTAACAGT ACTGTGTCAG AGTTTTTAAG TACAGGTGTA GTCATCCTCT GTCCCAGTCG
  1 D  I  V  M   T  Q  S   Q  K  F   M  S  T  S   V  G  D   R  V  S

 61 GTCACCTGCA AGGCCAGTCA GAATGTGGGT ACTAATGTAG CCTGGTATCA ACAGAAACCA
    CAGTGGACGT TCCGGTCAGT CTTACACCCA TGATTACATC GGACCATAGT TGTCTTTGGT
 21 V  T  C  K   A  S  Q   N  V  G   T  N  V  A   W  Y  Q   Q  K  P
             *   *  *  *   *  *  *   *  *  *  *
                           CDR #1

121 GGGCAATCTC CTAAAGCACT GATTTACTCG TCATCCTACC GGTACAGTGG AGTCCCTGAT
    CCCGTTAGAG GATTTCGTGA CTAAATGAGC AGTAGGATGG CCATGTCACC TCAGGGACTA
 41 G  Q  S  P   K  A  L   I  Y  S   S  S  Y  R   Y  S  G   V  P  D
                                 *   *  *  *  *   *  *
                                          CDR #2

181 CGCTTCACAG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCATCAGCCA TGTGCAGTCT
    GCGAAGTGTC CGTCACCTAG ACCCTGTCTA AAGTGAGAGT GGTAGTCGGT ACACGTCAGA
 61 R  F  T  G   S  G  S   G  T  D   F  T  L  T   I  S  H   V  Q  S

241 GAAGACTTGG CAGACTATTT CTGTCAGCAA TATAACATCT ATCCTCTCAC GTTCGGTCCT
    CTTCTGAACC GTCTGATAAA GACAGTCGTT ATATTGTAGA TAGGAGAGTG CAAGCCAGGA
 81 E  D  L  A   D  Y  F   C  Q  Q   Y  N  I  Y   P  L  T   F  G  P
                           *  *   *  *  *  *   *  *  *
                              CDR #3

301 GGGACCAAGC TGGAGTTGAA ACGGGCTGAT GCTGCACCAC CAACTGTATC CATCTTCCCA
    CCCTGGTTCG ACCTCAACTT TGCCCGACTA CGACGTGGTG GTTGACATAG GTAGAAGGGT
101 G  T  K  L   E  L  K   R  A  D   A  A  P  P   T  V  S   I  F  P

       BstBI
361 CCATTCGAA  (SEQ ID NO.16)
    GGTAAGCTT  (SEQ ID NO.17)
121 P  F  E
```

FIG. 16

```
  1 TTCTATTGCT ACAAACGCGT ACGCTGAGGT GCAGCTGGTG GAGTCTGGGG GAGGCTTAGT
    AAGATAACGA TGTTTGCGCA TGCGACTCCA CGTCGACCAC CTCAGACCCC CTCCGAATCA
  1                               E  V   Q  L  V   E  S  G  G   G  L  V

 61 GCCGCCTGGA GGGTCCCTGA AACTCTCCTG TGCAGCCTCT GGATTCATAT TCAGTAGTTA
    CGGCGGACCT CCCAGGGACT TTGAGAGGAC ACGTCGGAGA CCTAAGTATA AGTCATCAAT
 13  P  P  G   G  S  L  K   L  S  C   A  A  S   G  F  I  F   S  S  Y
                                                                 *  *
                                                        CDR #1

121 TGGCATGTCT TGGGTTCGCC AGACTCCAGG CAAGAGCCTG GAGTTGGTCG CAACCATTAA
    ACCGTACAGA ACCCAAGCGG TCTGAGGTCC GTTCTCGGAC CTCAACCAGC GTTGGTAATT
 33  G  M  S   W  V  R  Q   T  P  G   K  S  L   E  L  V  A   T  I  N
     *  *  *                                                 *  *  *

181 TAATAATGGT GATAGCACCT ATTATCCAGA CAGTGTGAAG GGCCGATTCA CCATCTCCCG
    ATTATTACCA CTATCGTGGA TAATAGGTCT GTCACACTTC CCGGCTAAGT GGTAGAGGGC
 53  N  N  G   D  S  T  Y   Y  P  D   S  V  K   G  R  F  T   I  S  R
     *  *  *   *  *  *  *   *  *  *   *  *  *
                  CDR #2

241 AGACAATGCC AAGAACACCC TGTACCTGCA AATGAGCAGT CTGAAGTCTG AGGACACAGC
    TCTGTTACGG TTCTTGTGGG ACATGGACGT TTACTCGTCA GACTTCAGAC TCCTGTGTCG
 73  D  N  A   K  N  T  L   Y  L  Q   M  S  S   L  K  S  E   D  T  A

301 CATGTTTTAC TGTGCAAGAG CCCTCATTAG TTCGGCTACT TGGTTTGGTT ACTGGGGCCA
    GTACAAAATG ACACGTTCTC GGGAGTAATC AAGCCGATGA ACCAAACCAA TGACCCCGGT
 93  M  F  Y   C  A  R  A   L  I  S   S  A  T   W  F  G  Y   W  G  Q
                       *   *  *  *   *  *  *   *  *  *  *
                                  CDR #3

361 AGGGACTCTG GTCACTGTCT CTGCAGCCAA AACAACAGCC CCATCTGTCT
    TCCCTGAGAC CAGTGACAGA GACGTCGGTT TTGTTGTCGG GGTAGACAGA
113  G  T  L   V  T  V  S   A  A  K   T  T  A   P  S  V  Y

         ApaI
411    ATCCGGG (SEQ ID NO.18)
       TAGGCCC (SEQ ID NO.19)
130     P
```

FIG. 17

FIG. 18

VL.front 31-MER

5' ACAAACGCGTACGCTGATATCGTCATGACAG 3' (SEQ ID NO.20)

VL.rear 31-MER

5' GCAGCATCAGCTCTTCGAAGCTCCAGCTTGG 3' (SEQ ID NO.21)

VH.front.SPE 21-MER

5' CCACTAGTACGCAAGTTCACG 3' (SEQ ID NO.22)

VH.rear 33-MER

5' GATGGGCCCTTGGTGGAGGCTGCAGAGACAGTG 3' (SEQ ID NO.23)

```
  1 ATGAAGAAGA ATATCGCATT TCTTCTTGCA TCTATGTTCG TTTTTTCTAT TGCTACAAAC
    TACTTCTTCT TATAGCGTAA AGAAGAACGT AGATACAAGC AAAAAAGATA ACGATGTTTG
-23 M  K  K  N   I  A  F   L  L  A   S  M  F  V   F  S  I   A  T  N

 61 GCGTACGCTG ATATCGTCAT GACACAGTCT CAAAAATTCA TGTCCACATC AGTAGGAGAC
    CGCATGCGAC TATAGCAGTA CTGTGTCAGA GTTTTTAAGT ACAGGTGTAG TCATCCTCTG
 -3 A  Y  A  D   I  V  M   T  Q  S   Q  K  F  M   S  T  S   V  G  D

121 AGGGTCAGCG TCACCTGCAA GGCCAGTCAG AATGTGGGTA CTAATGTAGC CTGGTATCAA
    TCCCAGTCGC AGTGGACGTT CCGGTCAGTC TTACACCCAT GATTACATCG GACCATAGTT
 18 R  V  S  V   T  C  K   A  S  Q   N  V  G  T   N  V  A   W  Y  Q
                      *   *  *  *   *  *  *  *   *  *  *
                                    CDR #1

181 CAGAAACCAG GGCAATCTCC TAAAGCACTG ATTTACTCGT CATCCTACCG GTACAGTGGA
    GTCTTTGGTC CCGTTAGAGG ATTTCGTGAC TAAATGAGCA GTAGGATGGC CATGTCACCT
 38 Q  K  P  G   Q  S  P   K  A  L   I  Y  S  S   S  Y  R   Y  S  G
                                          *  *   *  *  *   *  *
                                                 CDR #2

241 GTCCCTGATC GCTTCACAGG CAGTGGATCT GGGACAGATT TCACTCTCAC CATCAGCCAT
    CAGGGACTAG CGAAGTGTCC GTCACCTAGA CCCTGTCTAA AGTGAGAGTG GTAGTCGGTA
 58 V  P  D  R   F  T  G   S  G  S   G  T  D  F   T  L  T   I  S  H

301 GTGCAGTCTG AAGACTTGGC AGACTATTTC TGTCAGCAAT ATAACATCTA TCCTCTCACG
    CACGTCAGAC TTCTGAACCG TCTGATAAAG ACAGTCGTTA TATTGTAGAT AGGAGAGTGC
 78 V  Q  S  E   D  L  A   D  Y  F   C  Q  Q  Y   N  I  Y   P  L  T
                                       *  *  *   *  *  *   *  *  *
                                                 CDR #3
                               BstBI
361 TTCGGTCCTG GGACCAAGCT GGAGCTTCGA AGAGCTGTGG CTGCACCATC TGTCTTCATC
    AAGCCAGGAC CCTGGTTCGA CCTCGAAGCT TCTCGACACC GACGTGGTAG ACAGAAGTAG
 98 F  G  P  G   T  K  L   E  L  R   R  A  V  A   A  P  S   V  F  I

421 TTCCCGCCAT CTGATGAGCA GTTGAAATCT GGAACTGCTT CTGTTGTGTG CCTGCTGAAT
    AAGGGCGGTA GACTACTCGT CAACTTTAGA CCTTGACGAA GACAACACAC GGACGACTTA
118 F  P  P  S   D  E  Q   L  K  S   G  T  A  S   V  V  C   L  L  N

481 AACTTCTATC CCAGAGAGGC CAAAGTACAG TGGAAGGTGG ATAACGCCCT CCAATCGGGT
    TTGAAGATAG GGTCTCTCCG GTTTCATGTC ACCTTCCACC TATTGCGGGA GGTTAGCCCA
138 N  F  Y  P   R  E  A   K  V  Q   W  K  V  D   N  A  L   Q  S  G

541 AACTCCCAGG AGAGTGTCAC AGAGCAGGAC AGCAAGGACA GCACCTACAG CCTCAGCAGC
    TTGAGGGTCC TCTCACAGTG TCTCGTCCTG TCGTTCCTGT CGTGGATGTC GGAGTCGTCG
158 N  S  Q  E   S  V  T   E  Q  D   S  K  D  S   T  Y  S   L  S  S

601 ACCCTGACGC TGAGCAAAGC AGACTACGAG AAACACAAAG TCTACGCCTG CGAAGTCACC
    TGGGACTGCG ACTCGTTTCG TCTGATGCTC TTTGTGTTTC AGATGCGGAC GCTTCAGTGG
178 T  L  T  L   S  K  A   D  Y  E   K  H  K  V   Y  A  C   E  V  T

661 CATCAGGGCC TGAGCTCGCC CGTCACAAAG AGCTTCAACA GGGGAGAGTG
    GTAGTCCCGG ACTCGAGCGG GCAGTGTTTC TCGAAGTTGT CCCCTCTCAC
198 H  Q  G  L   S  S  P   V  T  K   S  F  N  R   G  E  C (SEQ ID NO.25)

711   TTAA  (SEQ ID NO.24)
      AATT
216   O
```

FIG. 19

```
  1 ATGAAAAAGA ATATCGCATT TCTTCTTGCA TCTATGTTCG TTTTTTCTAT TGCTACAAAC
    TACTTTTTCT TATAGCGTAA AGAAGAACGT AGATACAAGC AAAAAAGATA ACGATGTTTG
-23 M  K  K  N   I  A  F   L  L  A   S  M  F  V   F  S  I   A  T  N

 61 GCGTACGCTG AGGTGCAGCT GGTGGAGTCT GGGGGAGGCT TAGTGCCGCC TGGAGGGTCC
    CGCATGCGAC TCCACGTCGA CCACCTCAGA CCCCCTCCGA ATCACGGCGG ACCTCCCAGG
 -3 A  Y  A  E   V  Q  L   V  E  S   G  G  G  L   V  P  P   G  G  S

121 CTGAAACTCT CCTGTGCAGC CTCTGGATTC ATATTCAGTA GTTATGGCAT GTCTTGGGTT
    GACTTTGAGA GGACACGTCG GAGACCTAAG TATAAGTCAT CAATACCGTA CAGAACCCAA
 18 L  K  L  S   C  A  A   S  G  F   I  F  S  S   Y  G  M   S  W  V
                                            *    *  *  *   *
                                       CDR #1

181 CGCCAGACTC CAGGCAAGAG CCTGGAGTTG GTCGCAACCA TTAATAATAA TGGTGATAGC
    GCGGTCTGAG GTCCGTTCTC GGACCTCAAC CAGCGTTGGT AATTATTATT ACCACTATCG
 38 R  Q  T  P   G  K  S   L  E  L   V  A  T  I   N  N  N   G  D  S
                                         *  *   *  *  *   *  *  *

241 ACCTATTATC CAGACAGTGT GAAGGGCCGA TTCACCATCT CCCGAGACAA TGCCAAGAAC
    TGGATAATAG GTCTGTCACA CTTCCCGGCT AAGTGGTAGA GGGCTCTGTT ACGGTTCTTG
 58 T  Y  Y  P   D  S  V   K  G  R   F  T  I  S   R  D  N   A  K  N
    *  *  *  *   *  *  *   *
      CDR #2

301 ACCCTGTACC TGCAAATGAG CAGTCTGAAG TCTGAGGACA CAGCCATGTT TTACTGTGCA
    TGGGACATGG ACGTTTACTC GTCAGACTTC AGACTCCTGT GTCGGTACAA AATGACACGT
 78 T  L  Y  L   Q  M  S   S  L  K   S  E  D  T   A  M  F   Y  C  A

361 AGAGCCCTCA TTAGTTCGGC TACTTGGTTT GGTTACTGGG GCCAAGGGAC TCTGGTCACT
    TCTCGGGAGT AATCAAGCCG ATGAACCAAA CCAATGACCC CGGTTCCCTG AGACCAGTGA
 98 R  A  L  I   S  S  A   T  W  F   G  Y  W  G   Q  G  T   L  V  T
       *  *  *   *  *  *   *  *  *   *  *
                 CDR #3
                           ApaI
421 GTCTCTGCAG CCTCCACCAA GGGCCCATCG GTCTTCCCCC TGGCACCCTC CTCCAAGAGC
    CAGAGACGTC GGAGGTGGTT CCCGGGTAGC CAGAAGGGGG ACCGTGGGAG GAGGTTCTCG
118 V  S  A  A   S  T  K   G  P  S   V  F  P  L   A  P  S   S  K  S

481 ACCTCTGGGG GCACAGCGGC CCTGGGCTGC CTGGTCAAGG ACTACTTCCC CGAACCGGTG
    TGGAGACCCC CGTGTCGCCG GGACCCGACG GACCAGTTCC TGATGAAGGG GCTTGGCCAC
138 T  S  G  G   T  A  A   L  G  C   L  V  K  D   Y  F  P   E  P  V

541 ACGGTGTCGT GGAACTCAGG CGCCCTGACC AGCGGCGTGC ACACCTTCCC GGCTGTCCTA
    TGCCACAGCA CCTTGAGTCC GCGGGACTGG TCGCCGCACG TGTGGAAGGG CCGACAGGAT
158 T  V  S  W   N  S  G   A  L  T   S  G  V  H   T  F  P   A  V  L

601 CAGTCCTCAG GACTCTACTC CCTCAGCAGC GTGGTGACCG TGCCCTCCAG CAGCTTGGGC
    GTCAGGAGTC CTGAGATGAG GGAGTCGTCG CACCACTGGC ACGGGAGGTC GTCGAACCCG
178 Q  S  S  G   L  Y  S   L  S  S   V  V  T  V   P  S  S   S  L  G
```

FIG. 20A

```
661 ACCCAGACCT ACATCTGCAA CGTGAATCAC AAGCCCAGCA ACACCAAGGT GGACAAGAAA
    TGGGTCTGGA TGTAGACGTT GCACTTAGTG TTCGGGTCGT TGTGGTTCCA CCTGTTCTTT
198 T  Q  T  Y   I  C  N   V  N  H   K  P  S  N   T  K  V   D  K  K

721 GTTGAGCCCA AATCTTGTGA CAAAACTCAC ACATGA     (SEQ ID NO.26)
    CAACTCGGGT TTAGAACACT GTTTTGAGTG TGTACT
218 V  E  P  K   S  C  D   K  T  H   T  O      (SEQ ID NO.27)
```

FIG. 20B

Light Chain Primers:

MKLC-1, 22mer

5' CAGTCCAACTGTTCAGGACGCC 3' (SEQ ID NO.1)

MKLC-2, 22mer

5' GTGCTGCTCATGCTGTAGGTGC 3' (SEQ ID NO.2)

MKLC-3, 23mer

5' GAAGTTGATGTCTTGTGAGTGGC 3' (SEQ ID NO.3)

Heavy Chain Primers:

IGG2AC-1, 24mer

5' GCATCCTAGAGTCACCGAGGAGCC 3' (SEQ ID NO.4)

IGG2AC-2, 22mer

5' CACTGGCTCAGGGAAATAACCC 3' (SEQ ID NO.5)

IGG2AC-3, 22mer

5' GGAGAGCTGGGAAGGTGTGCAC 3' (SEQ ID NO.6)

FIG. 21

```
Light chain forward primer

6G4.light.Nsi   36-MER

5' CCAATGCATACGCT GAC ATC GTG ATG ACC CAG ACC CC  3' (SEQ ID NO.28)
                   T   T           T       T          (SEQ ID NO.29)
                                   A       A          (SEQ ID NO.30)
Light chain reverse primer

6G4.light.Mun   35-MER

5' AGA TGT CAA TTG CTC ACT GGA TGG TGG GAA GAT GG 3' (SEQ ID NO.31)
```

FIG. 22

Heavy chain forward primer

6G4.heavy.Mlu 32-MER

```
5' CAAACGCGTACGCT GAG ATC CAG CTG CAG CAG  3' (SEQ ID NO.32)
                        T         C           (SEQ ID NO.33)
```

Heavy chain reverse primer

SL002B 39-MER

```
5' CGATGGGCCCGG ATAGACCGATGGGGCTGTTGTTTTGGC  3' (SEQ ID NO.11)
                      T                         (SEQ ID NO.15)
                      A                         (SEQ ID NO.14)
                      G                         (SEQ ID NO.13)
```

FIG. 23

```
70 G ATATCGTGAT GACACAGACA CCACTCTCCC TGCCTGTCAG TCTTGGAGAT
   C TATAGCACTA CTGTGTCTGT GGTGAGAGGG ACGGACAGTC AGAACCTCTA
1  D  I  V  M   T  Q  T   P  L  S  L   P  V  S   L  G  D

121 CAGGCCTCCA TCTCTTGCAG ATCTAGTCAG AGCCTTGTAC ACGGTATTGG AAACACCTAT
    GTCCGGAGGT AGAGAACGTC TAGATCAGTC TCGGAACATG TGCCATAACC TTTGTGGATA
18  Q  A  S  I   S  C  R   S  S  Q   S  L  V  H   G  I  G   N  T  Y
                       *   *  *  *   *  *  *  *   *  *  *   *  *  *
                                         CDR #1

181 TTACATTGGT ACCTGCAGAA GCCAGGCCAG TCTCCAAAGC TCCTGATCTA CAAAGTTTCC
    AATGTAACCA TGGACGTCTT CGGTCCGGTC AGAGGTTTCG AGGACTAGAT GTTTCAAAGG
38  L  H  W  Y   L  Q  K   P  G  Q   S  P  K  L   L  I  Y   K  V  S
    *  *                                                    *  *  *
                                                            CDR #2

241 AACCGATTTT CTGGGGTCCC AGACAGGTTC AGTGGCAGTG GATCAGGGAC AGATTTCACA
    TTGGCTAAAA GACCCCAGGG TCTGTCCAAG TCACCGTCAC CTAGTCCCTG TCTAAAGTGT
58  N  R  F  S   G  V  P   D  R  F   S  G  S  G   S  G  T   D  F  T
    *  *  *  *

301 CTCAGGATCA GCAGAGTGGA GGCTGAGGAT CTGGGACTTT ATTTCTGCTC TCAAAGTACA
    GAGTCCTAGT CGTCTCACCT CCGACTCCTA GACCCTGAAA TAAAGACGAG AGTTTCATGT
78  L  R  I  S   R  V  E   A  E  D   L  G  L  Y   F  C  S   Q  S  T
                                                      *   *  *  *
                                                        CDR #3

361 CATGTTCCGC TCACGTTCGG TGCTGGGACC AAGCTGGAGC TGAAACGGGC TGATGCTGCA
    GTACAAGGCG AGTGCAAGCC ACGACCCTGG TTCGACCTCG ACTTTGCCCG ACTACGACGT
98  H  V  P  L   T  F  G   A  G  T   K  L  E  L   K  R  A   D  A  A
    *  *  *  *   *

                                          MunI
421 CCAACTGTAT CCATCTTCCC ACCATCCAGT GAGCAATTGA  (SEQ ID NO.34)
    GGTTGACATA GGTAGAAGGG TGGTAGGTCA CTCGTTAACT
118 P  T  V  S   I  F  P   P  S  S   E  Q  L  K   (SEQ ID NO.35)
```

FIG. 24

```
 70 G AGATTCAGCT GCAGCAGTCT GGACCTGAGC TGATGAAGCC TGGGGCTTCA
    C TCTAAGTCGA CGTCGTCAGA CCTGGACTCG ACTACTTCGG ACCCCGAAGT
  1 E  I  Q  L   Q  Q  S   G  P  E  L   M  K  P   G  A  S

121 GTGAAGATAT CCTGCAAGGC TTCTGGTTAT TCATTCAGTA GCCACTACAT GCACTGGGTG
    CACTTCTATA GGACGTTCCG AAGACCAATA AGTAAGTCAT CGGTGATGTA CGTGACCCAC
 18 V  K  I  S   C  K  A   S  G  Y   S  F  S  S   H  Y  M   H  W  V
                                             *     *  *  *     *
                                        CDR #1

181 AAGCAGAGCC ATGGAAAGAG CCTTGAGTGG ATTGGCTACA TTGATCCTTC CAATGGTGAA
    TTCGTCTCGG TACCTTTCTC GGAACTCACC TAACCGATGT AACTAGGAAG GTTACCACTT
 38 K  Q  S  H   G  K  S   L  E  W   I  G  Y  I   D  P  S   N  G  E
                                          *  *     *  *  *   *  *  *
                                                     CDR #2

241 ACTACTTACA ACCAGAAATT CAAGGGCAAG GCCACATTGA CTGTAGACAC ATCTTCCAGC
    TGATGAATGT TGGTCTTTAA GTTCCCGTTC CGGTGTAACT GACATCTGTG TAGAAGGTCG
 58 T  T  Y  N   Q  K  F   K  G  K   A  T  L  T   V  D  T   S  S  S
    *  *  *  *   *  *  *   *  *

301 ACAGCCAACG TGCATCTCAG CAGCCTGACA TCTGATGACT CTGCAGTCTA TTTCTGTGCA
    TGTCGGTTGC ACGTAGAGTC GTCGGACTGT AGACTACTGA GACGTCAGAT AAAGACACGT
 78 T  A  N  V   H  L  S   S  L  T   S  D  D  S   A  V  Y   F  C  A

361 AGAGGGGACT ATAGATACAA CGGCGACTGG TTTTTCGATG TCTGGGGCGC AGGGACCACG
    TCTCCCCTGA TATCTATGTT GCCGCTGACC AAAAAGCTAC AGACCCCGCG TCCCTGGTGC
 98 R  G  D  Y   R  Y  N   G  D  W   F  F  D  V   W  G  A   G  T  T
       *  *  *   *  *  *   *  *  *   *  *  *  *
                    CDR #3
      BstEII                                               ApaI
421 GTCACCGTCT CCTCCGCCAA AACCGACAGC CCCATCGGTC TATCCGGGCC
    CAGTGGCAGA GGAGGCGGAT TTGGCTGTCG GGGTAGCCAG ATAGGCCCGG
118 V  T  V  S   S  A  K   T  D  S   P  I  G  L   S  G  P

471 CATC  (SEQ ID NO.36)
    GTAG
135  I    (SEQ ID NO.37)
```

FIG. 25

5' CTTGGTGGAGGCGGAGGAGACG 3' (SEQ ID NO.38)

Mutagenesis Primer for 6G425VL

DS/VF 38MER

5' GAAACGGGCTGTTGCTGCACCAACTGTATTCATCTTCC 3' (SEQ ID NO.39)

SYN.BstEII 31 MER

5' GTCACCGTCT CCTCCGCCTC CACCAAGGGC C 3' (SEQ ID NO.40)

SYN.Apa 22 MER

5' CTTGGTGGAGGCGGAGGAGACG 3' (SEQ ID NO.38)

FIG. 26

```
  1 ATGAAGAAGA ATATCGCATT TCTTCTTGCA TCTATGTTCG TTTTTTCTAT TGCTACAAAT
    TACTTCTTCT TATAGCGTAA AGAAGAACGT AGATACAAGC AAAAAAGATA ACGATGTTTA
-23 M  K  K  N   I  A  F   L  L  A   S  M  F  V   F  S  I   A  T  N

 61 GCATACGCTG ATATCGTGAT GACACAGACA CCACTCTCCC TGCCTGTCAG TCTTGGAGAT
    CGTATGCGAC TATAGCACTA CTGTGTCTGT GGTGAGAGGG ACGGACAGTC AGAACCTCTA
 -3 A  Y  A  D   I  V  M   T  Q  T   P  L  S  L   P  V  S   L  G  D

121 CAGGCCTCCA TCTCTTGCAG ATCTAGTCAG AGCCTTGTAC ACGGTATTGG AAACACCTAT
    GTCCGGAGGT AGAGAACGTC TAGATCAGTC TCGGAACATG TGCCATAACC TTTGTGGATA
 18 Q  A  S  I   S  C  R   S  S  Q   S  L  V  H   G  I  G   N  T  Y
                       *   *  *  *   *  *  *  *   *  *  *   *  *  *
                                        CDR #1

181 TTACATTGGT ACCTGCAGAA GCCAGGCCAG TCTCCAAAGC TCCTGATCTA CAAAGTTTCC
    AATGTAACCA TGGACGTCTT CGGTCCGGTC AGAGGTTTCG AGGACTAGAT GTTTCAAAGG
 38 L  H  W  Y   L  Q  K   P  G  Q   S  P  K  L   L  I  Y   K  V  S
    *  *                                                     *  *  *
                                                             CDR #2

241 AACCGATTTT CTGGGGTCCC AGACAGGTTC AGTGGCAGTG GATCAGGGAC AGATTTCACA
    TTGGCTAAAA GACCCCAGGG TCTGTCCAAG TCACCGTCAC CTAGTCCCTG TCTAAAGTGT
 58 N  R  F  S   G  V  P   D  R  F   S  G  S  G   S  G  T   D  F  T
    *  *  *  *

301 CTCAGGATCA GCAGAGTGGA GGCTGAGGAT CTGGGACTTT ATTTCTGCTC TCAAAGTACA
    GAGTCCTAGT CGTCTCACCT CCGACTCCTA GACCCTGAAA TAAAGACGAG AGTTTCATGT
 78 L  R  I  S   R  V  E   A  E  D   L  G  L  Y   F  C  S   Q  S  T
                                                      *   *  *  *
                                                       CDR #3

361 CATGTTCCGC TCACGTTCGG TGCTGGGACC AAGCTGGAGC TGAAACGGGC TGTTGCTGCA
    GTACAAGGCG AGTGCAAGCC ACGACCCTGG TTCGACCTCG ACTTTGCCCG ACAACGACGT
 98 H  V  P  L   T  F  G   A  G  T   K  L  E  L   K  R  A   V  A  A
    *  *  *  *   *

421 CCAACTGTAT TCATCTTCCC ACCATCCAGT GAGCAATTGA AATCTGGAAC TGCCTCTGTT
    GGTTGACATA AGTAGAAGGG TGGTAGGTCA CTCGTTAACT TTAGACCTTG ACGGAGACAA
118 P  T  V  F   I  F  P   P  S  S   E  Q  L  K   S  G  T   A  S  V

481 GTGTGCCTGC TGAATAACTT CTATCCCAGA GAGGCCAAAG TACAGTGGAA GGTGGATAAC
    CACACGGACG ACTTATTGAA GATAGGGTCT CTCCGGTTTC ATGTCACCTT CCACCTATTG
138 V  C  L  L   N  N  F   Y  P  R   E  A  K  V   Q  W  K   V  D  N

541 GCCCTCCAAT CGGGTAACTC CCAGGAGAGT GTCACAGAGC AGGACAGCAA GGACAGCACC
    CGGGAGGTTA GCCCATTGAG GGTCCTCTCA CAGTGTCTCG TCCTGTCGTT CCTGTCGTGG
158 A  L  Q  S   G  N  S   Q  E  S   V  T  E  Q   D  S  K   D  S  T

601 TACAGCCTCA GCAGCACCCT GACGCTGAGC AAAGCAGACT ACGAGAAACA CAAAGTCTAC
    ATGTCGGAGT CGTCGTGGGA CTGCGACTCG TTTCGTCTGA TGCTCTTTGT GTTTCAGATG
178 Y  S  L  S   S  T  L   T  L  S   K  A  D  Y   E  K  H   K  V  Y
```

FIG. 27A

```
661 GCCTGCGAAG TCACCCATCA GGGCCTGAGC TCGCCCGTCA CAAAGAGCTT CAACAGGGGA
    CGGACGCTTC AGTGGGTAGT CCCGGACTCG AGCGGGCAGT GTTTCTCGAA GTTGTCCCCT
198 A  C  E  V   T  H  Q   G  L  S   S  P  V  T   K  S  F   N  R  G

721 GAGTGTTAA   (SEQ ID NO.41)
    CTCACAATT
218 E  C  O     (SEQ ID NO.42)
```

FIG. 27B

1 ATGAAAAAGA ATATCGCATT TCTTCTTGCA TCTATGTTCG TTTTTTCTAT TGCTACAAAC
TACTTTTTCT TATAGCGTAA AGAAGAACGT AGATACAAGC AAAAAAGATA ACGATGTTTG
-23 M K K N I A F L L A S M F V F S I A T N

61 GCGTACGCTG AGATTCAGCT GCAGCAGTCT GGACCTGAGC TGATGAAGCC TGGGGCTTCA
CGCATGCGAC TCTAAGTCGA CGTCGTCAGA CCTGGACTCG ACTACTTCGG ACCCCGAAGT
-3 A Y A E I Q L Q Q S G P E L M K P G A S

121 GTGAAGATAT CCTGCAAGGC TTCTGGTTAT TCATTCAGTA GCCACTACAT GCACTGGGTG
CACTTCTATA GGACGTTCCG AAGACCAATA AGTAAGTCAT CGGTGATGTA CGTGACCCAC
18 V K I S C K A S G Y S F S S H Y M H W V
* * * * *
CDR #1

181 AAGCAGAGCC ATGGAAAGAG CCTTGAGTGG ATTGGCTACA TTGATCCTTC CAATGGTGAA
TTCGTCTCGG TACCTTTCTC GGAACTCACC TAACCGATGT AACTAGGAAG GTTACCACTT
38 K Q S H G K S L E W I G Y I D P S N G E
* * * * * * * *
CDR #2

241 ACTACTTACA ACCAGAAATT CAAGGGCAAG GCCACATTGA CTGTAGACAC ATCTTCCAGC
TGATGAATGT TGGTCTTTAA GTTCCCGTTC CGGTGTAACT GACATCTGTG TAGAAGGTCG
58 T T Y N Q K F K G K A T L T V D T S S S
* * * * * * * * *

301 ACAGCCAACG TGCATCTCAG CAGCCTGACA TCTGATGACT CTGCAGTCTA TTTCTGTGCA
TGTCGGTTGC ACGTAGAGTC GTCGGACTGT AGACTACTGA GACGTCAGAT AAAGACACGT
78 T A N V H L S S L T S D D S A V Y F C A

361 AGAGGGGACT ATAGATACAA CGGCGACTGG TTTTTCGATG TCTGGGGCGC AGGGACCACG
TCTCCCCTGA TATCTATGTT GCCGCTGACC AAAAAGCTAC AGACCCCGCG TCCCTGGTGC
98 R G D Y R Y N G D W F F D V W G A G T T
* * * * * * * * * * * * *
CDR #3

421 GTCACCGTCT CCTCCGCCTC CACCAAGGGC CCATCGGTCT TCCCCCTGGC ACCCTCCTCC
CAGTGGCAGA GGAGGCGGAG GTGGTTCCCG GGTAGCCAGA AGGGGGACCG TGGGAGGAGG
118 V T V S *S A S T K G P S V F P L A P S S*

481 AAGAGCACCT CTGGGGGCAC AGCGGCCCTG GGCTGCCTGG TCAAGGACTA CTTCCCCGAA
TTCTCGTGGA GACCCCCGTG TCGCCGGGAC CCGACGGACC AGTTCCTGAT GAAGGGGCTT
138 *K S T S G G T A A L G C L V K D Y F P E*

541 CCGGTGACGG TGTCGTGGAA CTCAGGCGCC CTGACCAGCG GCGTGCACAC CTTCCCGGCT
GGCCACTGCC ACAGCACCTT GAGTCCGCGG GACTGGTCGC CGCACGTGTG GAAGGGCCGA
158 *P V T V S W N S G A L T S G V H T F P A*

601 GTCCTACAGT CCTCAGGACT CTACTCCCTC AGCAGCGTGG TGACCGTGCC CTCCAGCAGC
CAGGATGTCA GGAGTCCTGA GATGAGGGAG TCGTCGCACC ACTGGCACGG GAGGTCGTCG
178 *V L Q S S G L Y S L S S V V T V P S S S*

FIG. 28A

```
661 TTGGGCACCC AGACCTACAT CTGCAACGTG AATCACAAGC CCAGCAACAC CAAGGTGGAC
    AACCCGTGGG TCTGGATGTA GACGTTGCAC TTAGTGTTCG GGTCGTTGTG GTTCCACCTG
198 L  G  T  Q   T  Y  I   C  N  V   N  H  K  P   S  N  T   K  V  D

721 AAGAAAGTTG AGCCCAAATC TTGTGACAAA ACTCACACAT GA  (SEQ ID NO.43)
    TTCTTTCAAC TCGGGTTTAG AACACTGTTT TGAGTGTGTA CT
218 K  K  V  E   P  K  S   C  D  K   T  H  T  O      (SEQ ID NO.44)
```

FIG. 28B

Variable Light Chain Domain

```
                  10        20       abcde 30        40
6G425     DIVMTQTPLSLPVSLGDQASISCRSSQSLVHGIGNTYLHWYLQKPGQSPKLLIY
            #   # #  ## #  ### #                   #     ##
F(ab)-1   DIQMTQSPSSLSASVGDRVTITCRSSQSLVHGIGNTYLHWYQQKPGKAPKLLIY
                                    # ##########
humκI     DIQMTQSPSSLSASVGDRVTITCRASKTI-----SKYLAWYQQKPGKAPKLLIY
                                    ============
                                 ++++++++++++++++
                                         L1

          50        60        70        80        90       100
6G425     YKVSNRFSGVPDRFSDSGSGTDFTLRISRVEAEDLGLYFCSQSTHVPLTFGAGTKLELKR (SEQ ID NO.45)
                     #   #         #  ##### ### #            #   # #
F(ab)-1   YKVSNRFSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCSQSTHVPLTFGQGTKVEIKR (SEQ ID NO.46)
           ## ###                                 # ####
humκI     YSGSTLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQHNEYPLTFGQGTKVEIKR (SEQ ID NO.47)
           ===                                      ======
           +++++++                                +++++++++
                L2                                     L3
```

Variable Heavy Chain Domain

```
                  10        20        30        40
6G425     EIQLQQSGPELMKPGASVKISCKASGYSFSSHYMHWVKQSHGKSLEWI
           #  ##  ## ##  # ###  #              # ##  #   #
F(ab)-1   EVQLVESGGGLVQPGGSLRLSCAASGYSFSSHYMHWVRQAPGKGLEWV
                                    #  ## # #
humIII    EVQLVESGGGLVQPGGSLRLSCAASGFSFTGHWMNWVRQAPGKGLEWV
                                   =======
                                        +++++
                                       H1

          50  a                70        80  abc      90        100      110
6G425     GYIDPSNGETTYNQKFKGKATLTVDTSSSTANVHLSSLTSDDSAVYFCAARGDYRYNGDWFFDVWGAGT (SEQ ID NO.48)
                            ## ### # ## ###### ### #   #                   #
F(ab)-1   GYIDPSNGETTYNQKFKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAARGDYRYNGDWFFDVWGQGT (SEQ ID NO.49)
           # #  ##  # ####                                    # # # ###  #
humIII    GMIHPSDSETRYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAARGIYFY-GTTYFDYWGQGT (SEQ ID NO.50)
              ====                                            ===========
           +++++++++++++++++                                 +++++++++++++
                  H2                                               H3
```

FIG. 29

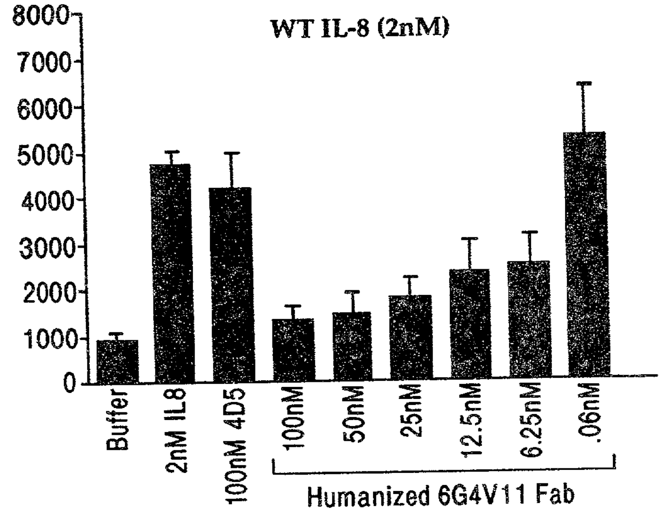


FIG. 30A

IC50~12nM

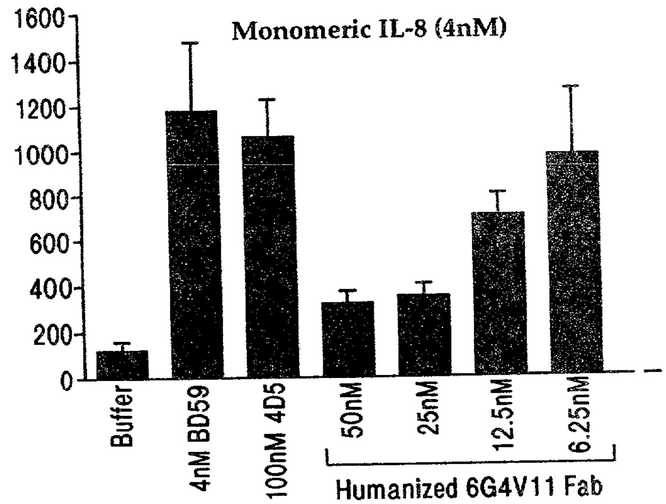


FIG. 30B

IC50~15nM

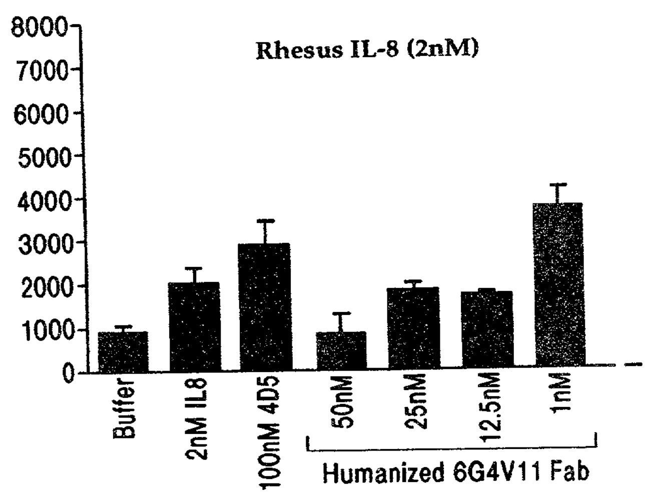


FIG. 30C

IC50~22nM

Amino Acid Sequence of the humanized anti-IL-8 6G4.2.5V11 Light Chain

MKKNIAFLLASMFVFSIATNAYADIQMTQSPSSLSASVGDRVTITCRSSQSLVHGIGNTY
LHWYQQKPGKAPKLLIYKVSNRFSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCSQST
HVPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN
ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG
EC (SEQ ID NO.51)

Amino Acid Sequence of the humanized anti-IL-8 6G4.2.5V11 Heavy Chain

MKKNIAFLLASMFVFSIATNAYAEVQLV**Q**SGGGLVQPGGSLRLSCAASGYSFSSHYMH
WVRQAPGKGLEWVGYIDPSNGETTYNQKFKGRFT**L**SRDNSKNT**A**YLQMNSLRAEDTAVYY
CARGDYRYNGDWFFDVWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF
PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK
VDKKVEPKSCDKTHT (SEQ ID NO.52)

Amino Acid Sequence of the peptide linker and M13 Phage Coat (gene-III)

SGGGSGSGDFDYEKMANANKGAMTENADENALQSDAKGKLDSVATDYGAAIDGFIGDVS
GLANGNGATGDFAGSSNSQMAQVGDGDNSPLMNNFRQYLPSLPQSVECRPFVFSAGKPY
EFSIDCDKINLFRGVFAFLLYVATFMYVFSTFANILRNKES (SEQ ID NO.53)

FIG. 31A

```
  1 ATGAAAAAGA ATATCGCATT TCTTCTTGCA TCTATGTTCG TTTTTTCTAT TGCTACAAAC
    TACTTTTTCT TATAGCGTAA AGAAGAACGT AGATACAAGC AAAAAAGATA ACGATGTTTG
-23 M  K  K  N   I  A  F   L  L  A   S  M  F  V   F  S  I   A  T  N

 61 GCATACGCTG ATATCCAGAT GACCCAGTCC CCGAGCTCCC TGTCCGCCTC TGTGGGCGAT
    CGTATGCGAC TATAGGTCTA CTGGGTCAGG GGCTCGAGGG ACAGGCGGAG ACACCCGCTA
 -3 A  Y  A  D   I  Q  M   T  Q  S   P  S  S  L   S  A  S   V  G  D

121 AGGGTCACCA TCACCTGCAG GTCAAGTCAA AGCTTAGTAC ATGGTATAGG TAACACGTAT
    TCCCAGTGGT AGTGGACGTC CAGTTCAGTT TCGAATCATG TACCATATCC ACGATGCATA
 18 R  V  T  I   T  C  R   S  S  Q   S  L  V  H   G  I  G   N  T  Y

181 TTACACTGGT ATCAACAGAA ACCAGGAAAA GCTCCGAAAC TACTGATTTA CAAAGTATCC
    AATGTGACCA TAGTTGTCTT TGGTCCTTTT CGAGGCTTTG ATGACTAAAT GTTTCATAGG
 38 L  H  W  Y   Q  Q  K   P  G  K   A  P  K  L   L  I  Y   K  V  S

241 AATCGATTCT CTGGAGTCCC TTCTCGCTTC TCTGGATCCG GTTCTGGGAC GGATTTCACT
    TTAGCTAAGA GACCTCAGGG AAGAGCGAAG AGACCTAGGC CAAGACCCTG CCTAAAGTGA
 58 N  R  F  S   G  V  P   S  R  F   S  G  S  G   S  G  T   D  F  T

301 CTGACCATCA GCAGTCTGCA GCCAGAAGAC TTCGCAACTT ATTACTGTTC ACAGAGTACT
    GACTGGTAGT CGTCAGACGT CGGTCTTCTG AAGCGTTGAA TAATGACAAG TGTCTCATGA
 78 L  T  I  S   S  L  Q   P  E  D   F  A  T  Y   Y  C  S   Q  S  T

361 CATGTCCCGC TCACGTTTGG ACAGGGTACC AAGGTGGAGA TCAAACGAAC TGTGGCTGCA
    GTACAGGGCG AGTGCAAACC TGTCCCATGG TTCCACCTCT AGTTTGCTTG ACACCGACGT
 98 H  V  P  L   T  F  G   Q  G  T   K  V  E  I   K  R  T   V  A  A

421 CCATCTGTCT TCATCTTCCC GCCATCTGAT GAGCAGTTGA AATCTGGAAC TGCTTCTGTT
    GGTAGACAGA AGTAGAAGGG CGGTAGACTA CTCGTCAACT TTAGACCTTG ACGAAGACAA
118 P  S  V  F   I  F  P   P  S  D   E  Q  L  K   S  G  T   A  S  V

481 GTGTGCCTGC TGAATAACTT CTATCCCAGA GAGGCCAAAG TACAGTGGAA GGTGGATAAC
    CACACGGACG ACTTATTGAA GATAGGGTCT CTCCGGTTTC ATGTCACCTT CCACCTATTG
138 V  C  L  L   N  N  F   Y  P  R   E  A  K  V   Q  W  K   V  D  N

541 GCCCTCCAAT CGGGTAACTC CCAGGAGAGT GTCACAGAGC AGGACAGCAA GGACAGCACC
    CGGGAGGTTA GCCCATTGAG GGTCCTCTCA CAGTGTCTCG TCCTGTCGTT CCTGTCGTGG
158 A  L  Q  S   G  N  S   Q  E  S   V  T  E  Q   D  S  K   D  S  T

601 TACAGCCTCA GCAGCACCCT GACGCTGAGC AAAGCAGACT ACGAGAAACA CAAAGTCTAC
    ATGTCGGAGT CGTCGTGGGA CTGCGACTCG TTTCGTCTGA TGCTCTTTGT GTTTCAGATG
178 Y  S  L  S   S  T  L   T  L  S   K  A  D  Y   E  K  H   K  V  Y

661 GCCTGCGAAG TCACCCATCA GGGCCTGAGC TCGCCCGTCA CAAAGAGCTT CAACAGGGGA
    CGGACGCTTC AGTGGGTAGT CCCGGACTCG AGCGGGCAGT GTTTCTCGAA GTTGTCCCCT
198 A  C  E  V   T  H  Q   G  L  S   S  P  V  T   K  S  F   N  R  G
                                                        (SEQ ID NO.54)
721 GAGTGTTAAG CTGATCCTCT ACGCCGGACG CATCGTGGCC CTAGTACGCA ACTAGTCGTA
    CTCACAATTC GACTAGGAGA TGCGGCCTGC GTAGCACCGG GATCATGCGT TGATCAGCAT
218 E  C  O (SEQ ID NO.51)
```

FIG. 31B

Amino Acid Sequence of the humanized anti-IL-8 6G4.2.5V19 Light Chain

MKKNIAFLLASMFVFSIATNAYADIQMTQSPSSLSASVGDRVTITCRSSQSLVHGIGNTY
LHWYQQKPGKAPKLLIYKVSNRFSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCSQST
HVPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN
ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG
EC (SEQ ID NO.51)

Amino Acid Sequence of the humanized anti-IL-8 6G4.2.5V19 Heavy Chain

MKKNIAFLLASMFVFSIATNAYAEVQLVESGGGLVQPGGSLRLSCAASGYSFSSHYMH
WVKQ**A**PGKGLEWVGYIDPSNGETTYNQKFKGRFT**L**SRDNSKNT**A**YLQMNSLRAEDTAVYY
CARGDYRYNGDWFFDVWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF
PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK
VDKKVEPKSCDKTHT (SEQ ID NO.55)

FIG. 31C

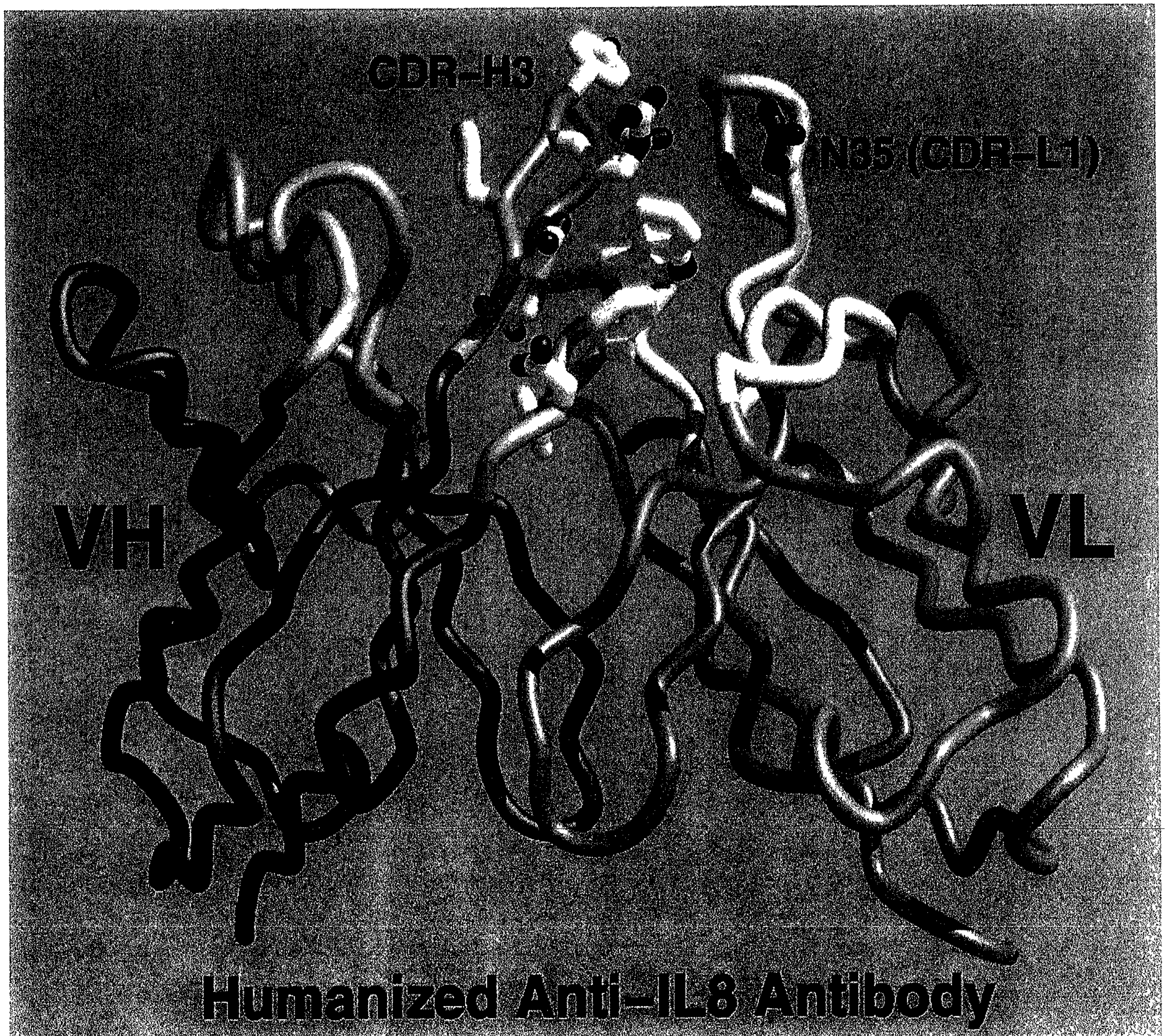


FIG. 32

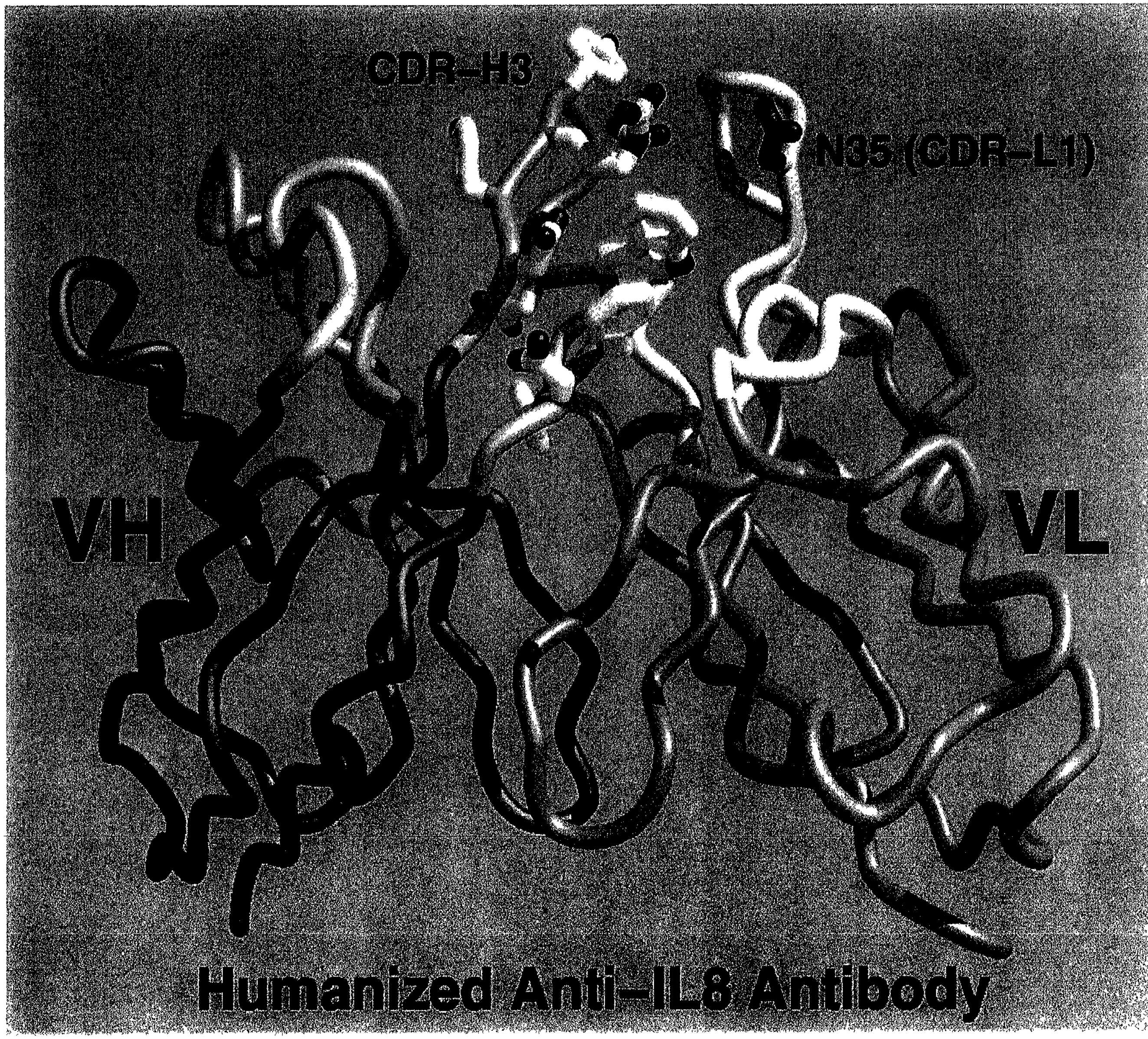


FIG. 32

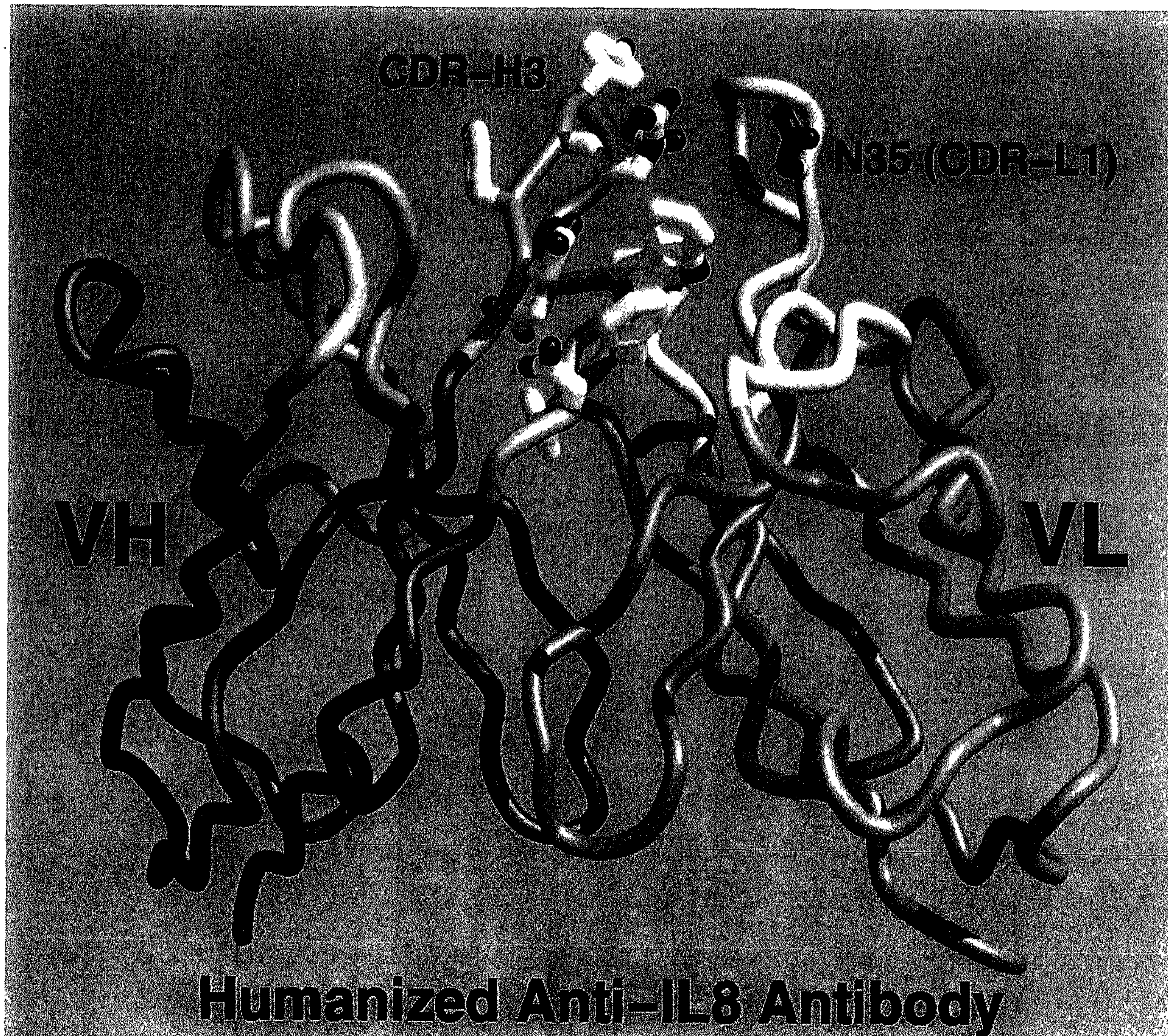


FIG. 32

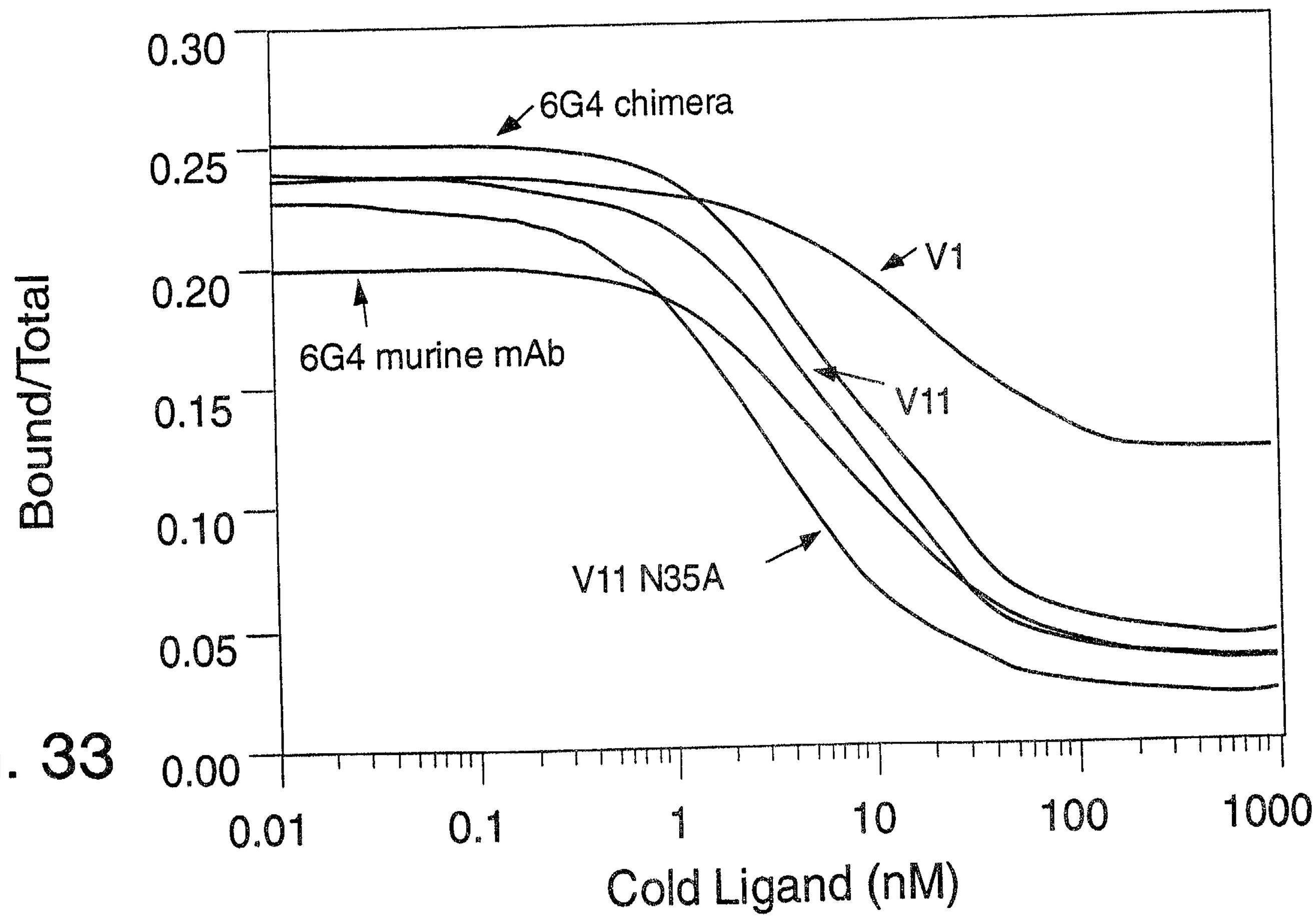

6G4 chimera
V1
V11
6G4 murine mAb
V11 N35A
Bound/Total
0.30
0.25
0.20
0.15
0.10
0.05
0.00
0.01
0.1
1
10
100
1000
Cold Ligand (nM)

FIG. 33

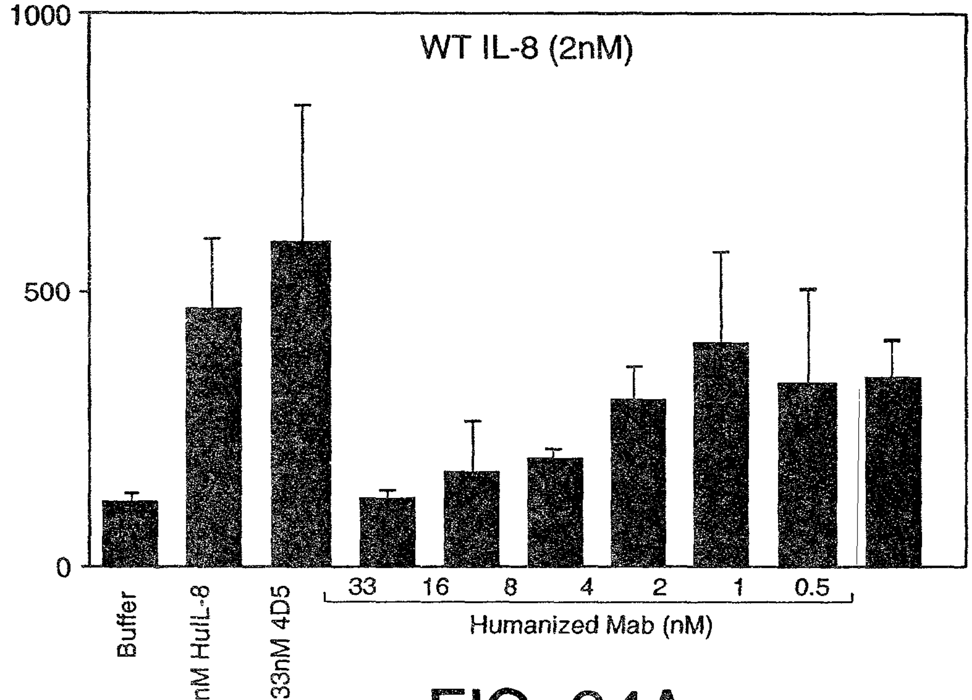


FIG. 34A

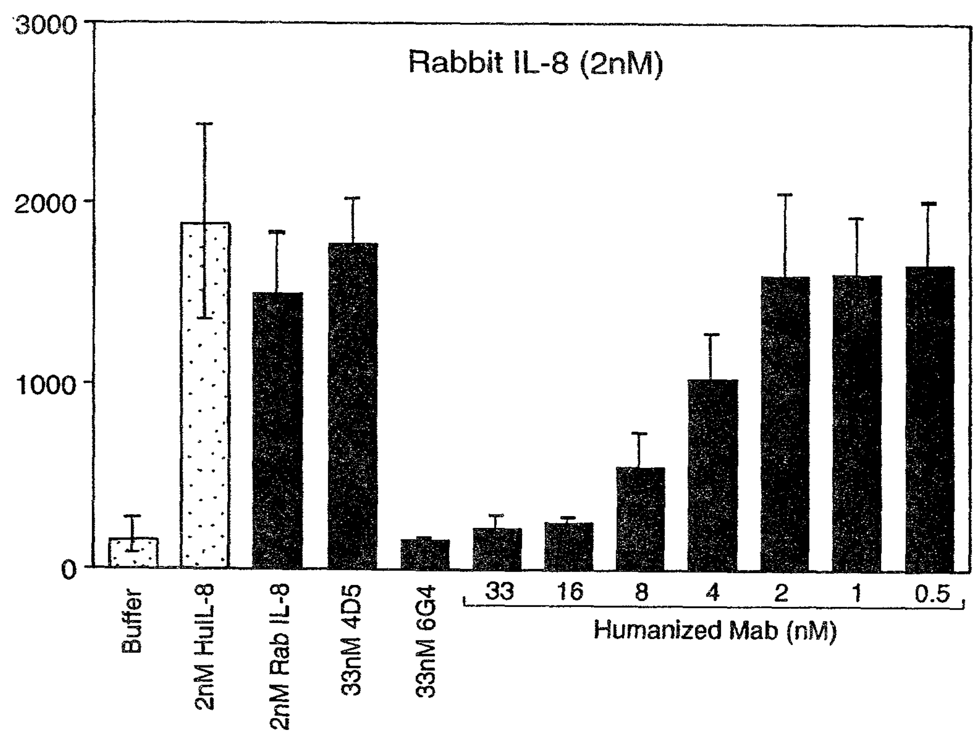


FIG. 34B

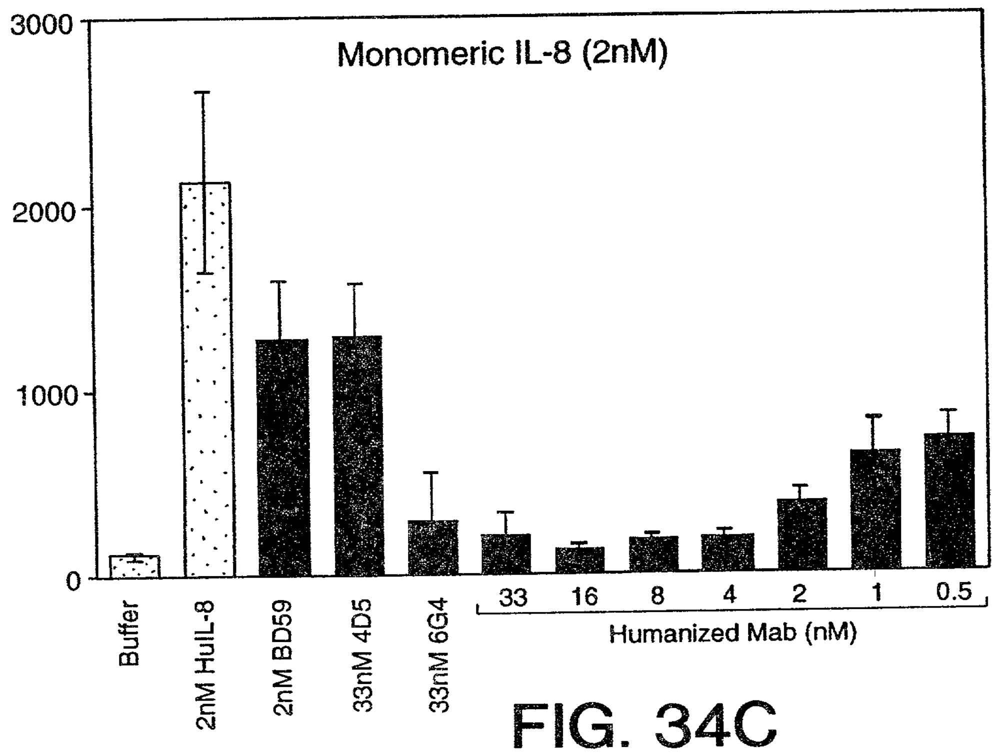


FIG. 34C

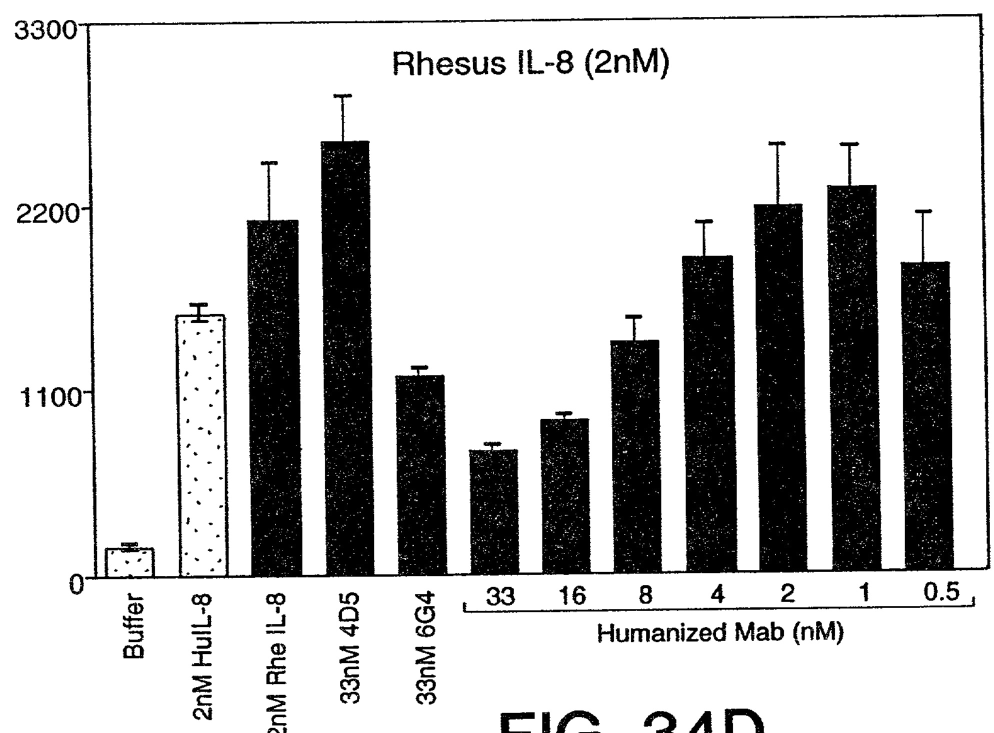


FIG. 34D

Amino Acid Sequence of the humanized anti-IL-8 6G4.2.5V11N35A Light Chain

MKKNIAFLLASMFVFSIATNAYADIQMTQSPSSLSASVGDRVTITCRSSQSLVHGIG**A**TY
LHWYQQKPGKAPKLLIYKVSNRFSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCSQST
HVPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN
ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG
EC (SEQ ID NO.56)

Amino Acid Sequence of the humanized anti-IL-8 6G4.2.5V11N35A Heavy Chain

MKKNIAFLLASMFVFSIATNAYAEVQLVQSGGGLVQPGGSLRLSCAASGYSFSSHYMH
WVRQAPGKGLEWVGYIDPSNGETTYNQKFKGRFTLSRDNSKNTAYLQMNSLRAEDTAVYY
CARGDYRYNGDWFFDVWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF
PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK
VDKKVEPKSCDKTHT (SEQ ID NO.52)

Amino Acid Sequence of the putative Pepsin Cleavage Site and GCN4 Leucine Zipper

CPPCPAPE<u>LL</u>GGRMKQLEDKVEELLSKNYHLENEVARLKKLVGER (SEQ ID NO.57)

FIG. 35

```
  1 ATGAAAAAGA ATATCGCATT TCTTCTTGCA TCTATGTTCG TTTTTTCTAT TGCTACAAAC
    TACTTTTTCT TATAGCGTAA AGAAGAACGT AGATACAAGC AAAAAAGATA ACGATGTTTG
-23 M  K  K  N   I  A  F   L  L  A   S  M  F  V   F  S  I   A  T  N

 61 GCATACGCTG ATATCCAGAT GACCCAGTCC CCGAGCTCCC TGTCCGCCTC TGTGGGCGAT
    CGTATGCGAC TATAGGTCTA CTGGGTCAGG GGCTCGAGGG ACAGGCGGAG ACACCCGCTA
 -3 A  Y  A  D   I  Q  M   T  Q  S   P  S  S  L   S  A  S   V  G  D

121 AGGGTCACCA TCACCTGCAG GTCAAGTCAA AGCTTAGTAC ATGGTATAGG TGCTACGTAT
    TCCCAGTGGT AGTGGACGTC CAGTTCAGTT TCGAATCATG TACCATATCC ACGATGCATA
 18 R  V  T  I   T  C  R   S  S  Q   S  L  V  H   G  I  G   A  T  Y

181 TTACACTGGT ATCAACAGAA ACCAGGAAAA GCTCCGAAAC TACTGATTTA CAAAGTATCC
    AATGTGACCA TAGTTGTCTT TGGTCCTTTT CGAGGCTTTG ATGACTAAAT GTTTCATAGG
 38 L  H  W  Y   Q  Q  K   P  G  K   A  P  K  L   L  I  Y   K  V  S

241 AATCGATTCT CTGGAGTCCC TTCTCGCTTC TCTGGATCCG GTTCTGGGAC GGATTTCACT
    TTAGCTAAGA GACCTCAGGG AAGAGCGAAG AGACCTAGGC CAAGACCCTG CCTAAAGTGA
 58 N  R  F  S   G  V  P   S  R  F   S  G  S  G   S  G  T   D  F  T

301 CTGACCATCA GCAGTCTGCA GCCAGAAGAC TTCGCAACTT ATTACTGTTC ACAGAGTACT
    GACTGGTAGT CGTCAGACGT CGGTCTTCTG AAGCGTTGAA TAATGACAAG TGTCTCATGA
 78 L  T  I  S   S  L  Q   P  E  D   F  A  T  Y   Y  C  S   Q  S  T

361 CATGTCCCGC TCACGTTTGG ACAGGGTACC AAGGTGGAGA TCAAACGAAC TGTGGCTGCA
    GTACAGGGCG AGTGCAAACC TGTCCCATGG TTCCACCTCT AGTTTGCTTG ACACCGACGT
 98 H  V  P  L   T  F  G   Q  G  T   K  V  E  I   K  R  T   V  A  A

421 CCATCTGTCT TCATCTTCCC GCCATCTGAT GAGCAGTTGA AATCTGGAAC TGCTTCTGTT
    GGTAGACAGA AGTAGAAGGG CGGTAGACTA CTCGTCAACT TTAGACCTTG ACGAAGACAA
118 P  S  V  F   I  F  P   P  S  D   E  Q  L  K   S  G  T   A  S  V

481 GTGTGCCTGC TGAATAACTT CTATCCCAGA GAGGCCAAAG TACAGTGGAA GGTGGATAAC
    CACACGGACG ACTTATTGAA GATAGGGTCT CTCCGGTTTC ATGTCACCTT CCACCTATTG
138 V  C  L  L   N  N  F   Y  P  R   E  A  K  V   Q  W  K   V  D  N

541 GCCCTCCAAT CGGGTAACTC CCAGGAGAGT GTCACAGAGC AGGACAGCAA GGACAGCACC
    CGGGAGGTTA GCCCATTGAG GGTCCTCTCA CAGTGTCTCG TCCTGTCGTT CCTGTCGTGG
158 A  L  Q  S   G  N  S   Q  E  S   V  T  E  Q   D  S  K   D  S  T

601 TACAGCCTCA GCAGCACCCT GACGCTGAGC AAAGCAGACT ACGAGAAACA CAAAGTCTAC
    ATGTCGGAGT CGTCGTGGGA CTGCGACTCG TTTCGTCTGA TGCTCTTTGT GTTTCAGATG
178 Y  S  L  S   S  T  L   T  L  S   K  A  D  Y   E  K  H   K  V  Y

661 GCCTGCGAAG TCACCCATCA GGGCCTGAGC TCGCCCGTCA CAAAGAGCTT CAACAGGGGA
    CGGACGCTTC AGTGGGTAGT CCCGGACTCG AGCGGGCAGT GTTTCTCGAA GTTGTCCCCT
198 A  C  E  V   T  H  Q   G  L  S   S  P  V  T   K  S  F   N  R  G
                                                        (SEQ ID NO.58)
721 GAGTGTTAAG CTGATCCTCT ACGCCGGACG CATCGTGGCC CTAGTACGCA ACTAGTCGTA
    CTCACAATTC GACTAGGAGA TGCGGCCTGC GTAGCACCGG GATCATGCGT TGATCAGCAT
218 E  C  O (SEQ ID NO.56)
```

FIG. 36

```
 781 AAAAGGGTAT CTAGAGGTTG AGGTGATTTT ATGAAAAAGA ATATCGCATT TCTTCTTGCA
     TTTTCCCATA GATCTCCAAC TCCACTAAAA TACTTTTTCT TATAGCGTAA AGAAGAACGT
  -1                                 M  K  K  N  I  A  F  L  L  A

 841 TCTATGTTCG TTTTTTCTAT TGCTACAAAC GCGTACGCTG AGGTTCAGCT AGTGCAGTCT
     AGATACAAGC AAAAAAGATA ACGATGTTTG CGCATGCGAC TCCAAGTCGA TCACGTCAGA
 -11 S  M  F  V  F  S  I  A  T  N  A  Y  A  E  V  Q  L  V  Q  S

 901 GGCGGTGGCC TGGTGCAGCC AGGGGGCTCA CTCCGTTTGT CCTGTGCAGC TTCTGGCTAC
     CCGCCACCGG ACCACGTCGG TCCCCCGAGT GAGGCAAACA GGACACGTCG AAGACCGATG
   8 G  G  G  L  V  Q  P  G  G  S  L  R  L  S  C  A  A  S  G  Y

 961 TCCTTCTCGA GTCACTATAT GCACTGGGTC CGTCAGGCCC CGGGTAAGGG CCTGGAATGG
     AGGAAGAGCT CAGTGATATA CGTGACCCAG GCAGTCCGGG GCCCATTCCC GGACCTTACC
  28 S  F  S  S  H  Y  M  H  W  V  R  Q  A  P  G  K  G  L  E  W

1021 GTTGGATATA TTGATCCTTC CAATGGTGAA ACTACGTATA ATCAAAAGTT CAAGGGCCGT
     CAACCTATAT AACTAGGAAG GTTACCACTT TGATGCATAT TAGTTTTCAA GTTCCCGGCA
  48 V  G  Y  I  D  P  S  N  G  E  T  T  Y  N  Q  K  F  K  G  R

1081 TTCACTTTAT CTCGCGACAA CTCCAAAAAC ACAGCATACC TGCAGATGAA CAGCCTGCGT
     AAGTGAAATA GAGCGCTGTT GAGGTTTTTG TGTCGTATGG ACGTCTACTT GTCGGACGCA
  68 F  T  L  S  R  D  N  S  K  N  T  A  Y  L  Q  M  N  S  L  R

1141 GCTGAGGACA CTGCCGTCTA TTACTGTGCA AGAGGGGATT ATCGCTACAA TGGTGACTGG
     CGACTCCTGT GACGGCAGAT AATGACACGT TCTCCCCTAA TAGCGATGTT ACCACTGACC
  88 A  E  D  T  A  V  Y  Y  C  A  R  G  D  Y  R  Y  N  G  D  W

1201 TTCTTCGACG TCTGGGGTCA AGGAACCCTG GTCACCGTCT CCTCGGCCTC CACCAAGGGC
     AAGAAGCTGC AGACCCCAGT TCCTTGGGAC CAGTGGCAGA GGAGCCGGAG GTGGTTCCCG
 108 F  F  D  V  W  G  Q  G  T  L  V  T  V  S  S  A  S  T  K  G

1261 CCATCGGTCT TCCCCCTGGC ACCCTCCTCC AAGAGCACCT CTGGGGGCAC AGCGGCCCTG
     GGTAGCCAGA AGGGGGACCG TGGGAGGAGG TTCTCGTGGA GACCCCCGTG TCGCCGGGAC
 128 P  S  V  F  P  L  A  P  S  S  K  S  T  S  G  G  T  A  A  L

1321 GGCTGCCTGG TCAAGGACTA CTTCCCCGAA CCGGTGACGG TGTCGTGGAA CTCAGGCGCC
     CCGACGGACC AGTTCCTGAT GAAGGGGCTT GGCCACTGCC ACAGCACCTT GAGTCCGCGG
 148 G  C  L  V  K  D  Y  F  P  E  P  V  T  V  S  W  N  S  G  A

1381 CTGACCAGCG GCGTGCACAC CTTCCCGGCT GTCCTACAGT CCTCAGGACT CTACTCCCTC
     GACTGGTCGC CGCACGTGTG GAAGGGCCGA CAGGATGTCA GGAGTCCTGA GATGAGGGAG
 168 L  T  S  G  V  H  T  F  P  A  V  L  Q  S  S  G  L  Y  S  L

1441 AGCAGCGTGG TGACCGTGCC CTCCAGCAGC TTGGGCACCC AGACCTACAT CTGCAACGTG
     TCGTCGCACC ACTGGCACGG GAGGTCGTCG AACCCGTGGG TCTGGATGTA GACGTTGCAC
 188 S  S  V  V  T  V  P  S  S  S  L  G  T  Q  T  Y  I  C  N  V

1501 AATCACAAGC CCAGCAACAC CAAGGTCGAC AAGAAAGTTG AGCCCAAATC TTGTGACAAA
     TTAGTGTTCG GGTCGTTGTG GTTCCAGCTG TTCTTTCAAC TCGGGTTTAG AACACTGTTT
 208 N  H  K  P  S  N  T  K  V  D  K  K  V  E  P  K  S  C  D  K

1561 ACTCACACAT GCCCGCCGTG CCCAGCACCA GAACTGCTGG GCGGCCGCAT GAAACAGCTA
     TGAGTGTGTA CGGGCGGCAC GGGTCGTGGT CTTGACGACC CGCCGGCGTA CTTTGTCGAT
 228 T  H  T  C  P  P  C  P  A  P  E  L  L  G  G  R  M  K  Q  L
```

FIG. 37A

```
1621 GAGGACAAGG TCGAAGAGCT ACTCTCCAAG AACTACCACC TAGAGAATGA AGTGGCAAGA
     CTCCTGTTCC AGCTTCTCGA TGAGAGGTTC TTGATGGTGG ATCTCTTACT TCACCGTTCT
 248 E  D  K  V   E  E  L   L  S  K   N  Y  H  L   E  N  E   V  A  R

1681 CTCAAAAAGC TTGTCGGGGA GCGCTAA   (SEQ ID NO.59)
     GAGTTTTTCG AACAGCCCCT CGCGATT
 268 L  K  K  L   V  G  E   R  O     (SEQ ID NO.60)
```

FIG. 37B

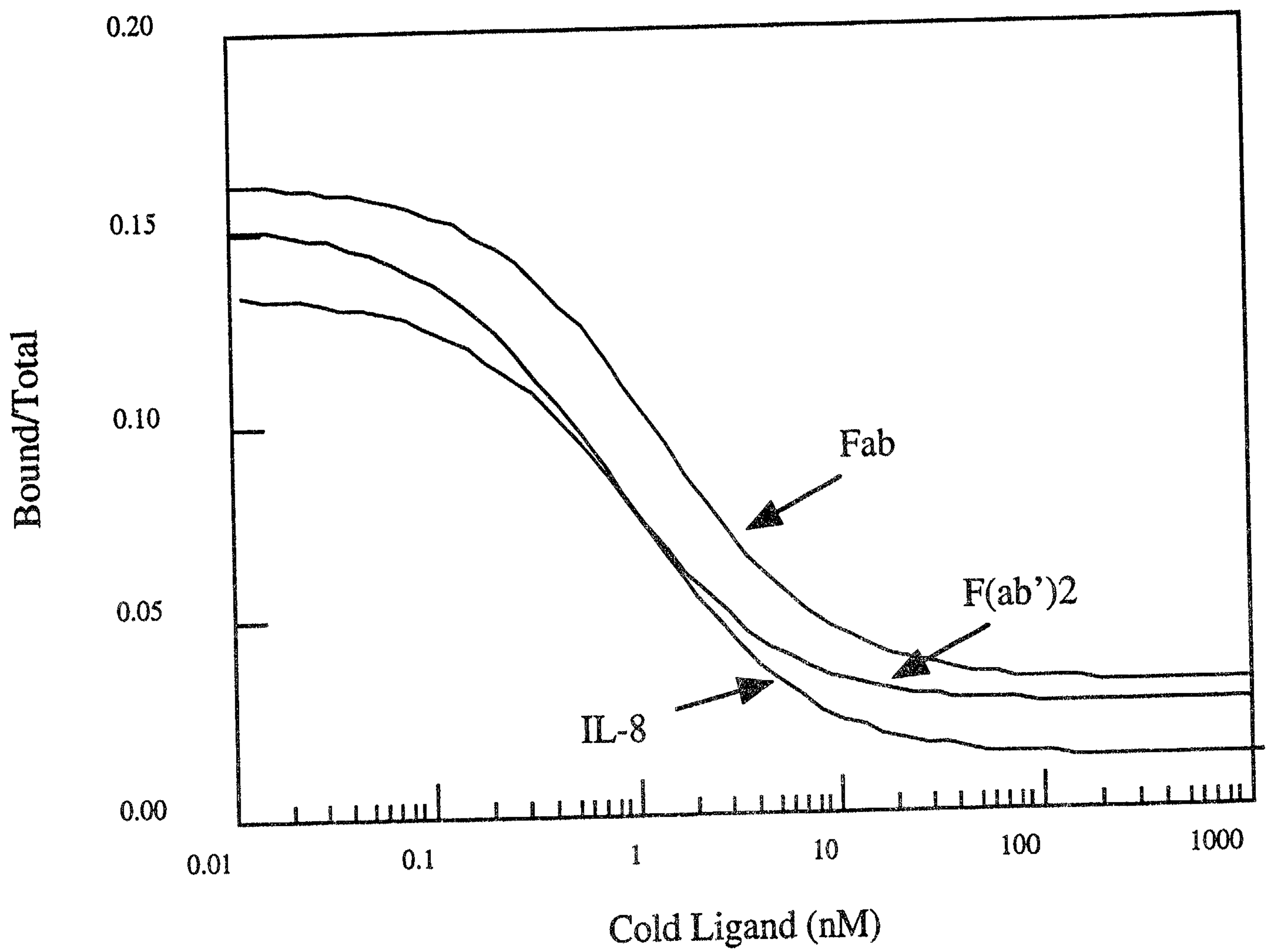

0.20
0.15
0.10
0.05
0.00
Bound/Total
Fab
F(ab')2
IL-8
0.01
0.1
1
10
100
1000
Cold Ligand (nM)

FIG. 38

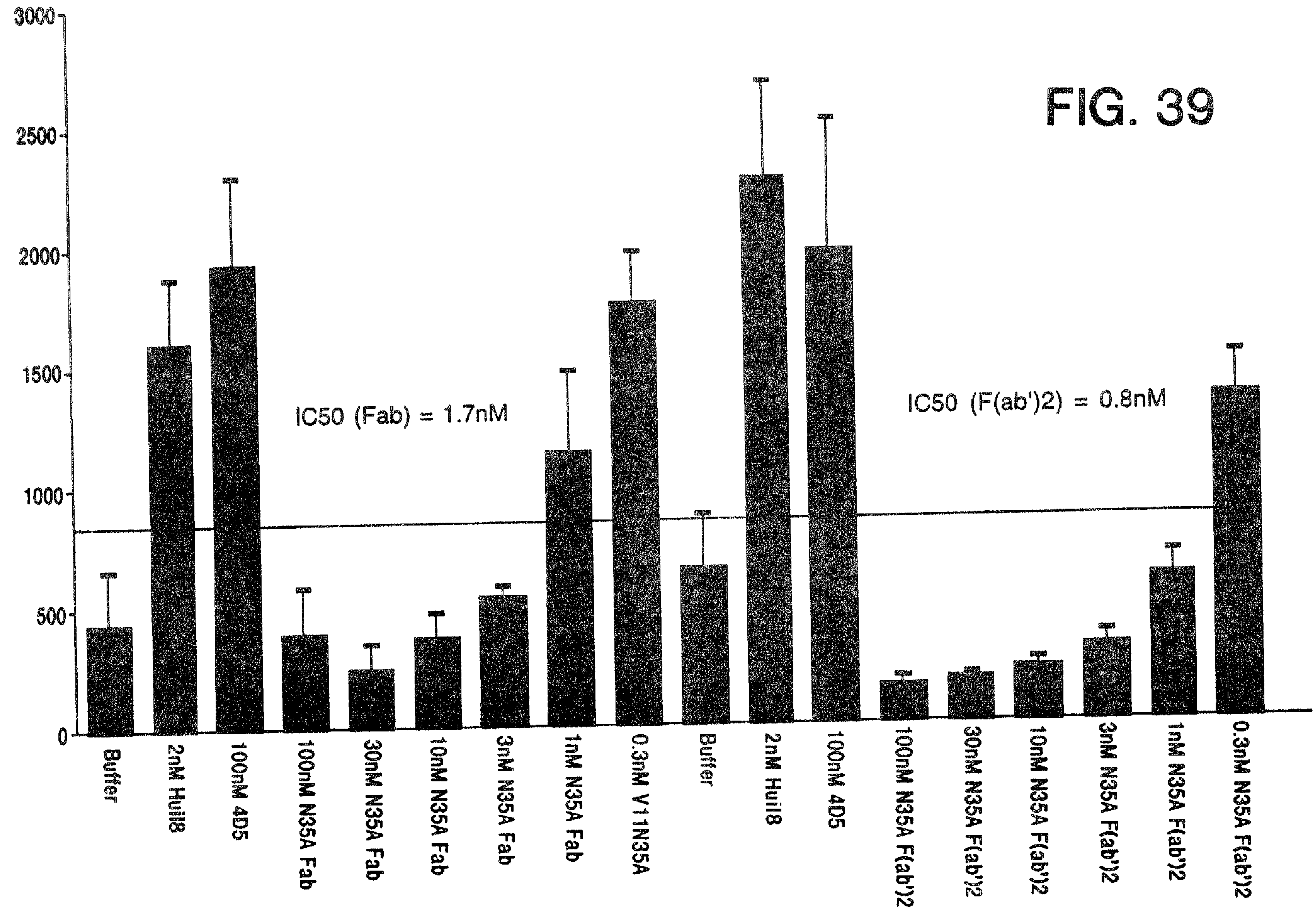
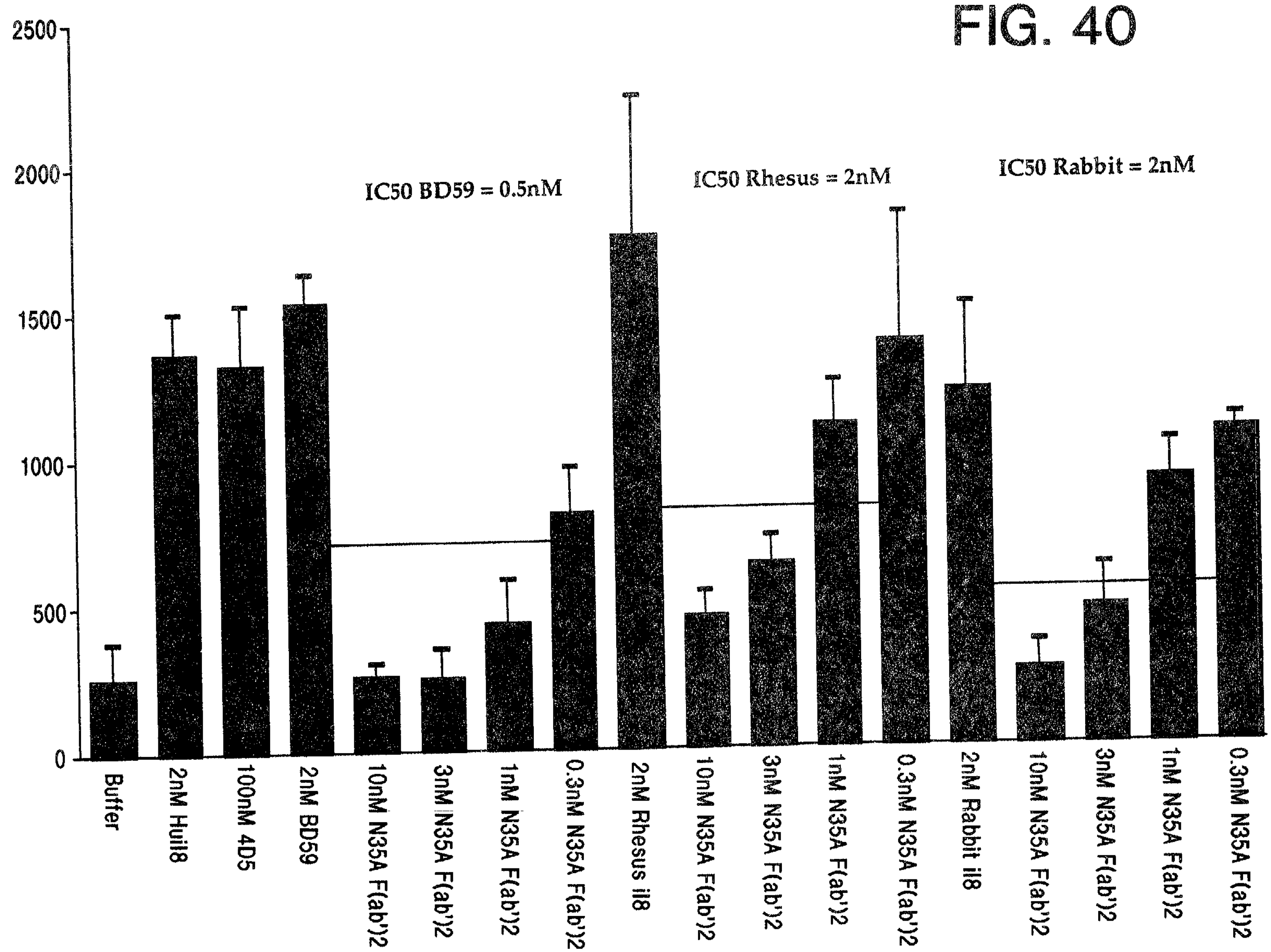

3000
2500
2000
1500
1000
500
0
IC50 (Fab) = 1.7nM
IC50 (F(ab')2) = 0.8nM
Buffer
2nM Huil8
100nM 4D5
100nM N35A Fab
30nM N35A Fab
10nM N35A Fab
3nM N35A Fab
1nM N35A Fab
0.3nM V11N35A
Buffer
2nM Huil8
100nM 4D5
100nM N35A F(ab')2
30nM N35A F(ab')2
10nM N35A F(ab')2
3nM N35A F(ab')2
1nM N35A F(ab')2
0.3nM N35A F(ab')2

FIG. 39

FIG. 40



2500
2000
1500
1000
500
0
IC50 BD59 = 0.5nM
IC50 Rhesus = 2nM
IC50 Rabbit = 2nM
Buffer
2nM Huil8
100nM 4D5
2nM BD59
10nM N35A F(ab')2
3nM N35A F(ab')2
1nM N35A F(ab')2
0.3nM N35A F(ab')2
2nM Rhesus il8
10nM N35A F(ab')2
3nM N35A F(ab')2
1nM N35A F(ab')2
0.3nM N35A F(ab')2
2nM Rabbit il8
10nM N35A F(ab')2
3nM N35A F(ab')2
1nM N35A F(ab')2
0.3nM N35A F(ab')2

```
                                                                         aluI                   pleI
                                                                        hindIII               mboII  taqI
                                                          ddeI       tru9I                    earI/ksp632I
 ecoRI        pflMI                                                  mseI cac8I             mboII  hinfI
 apoI         bslI                          nlaIII       bsrDI
1 GAATTCAACT TCTCCATACT TTGGATAAGG AAATACAGAC ATGAAAAATC TCATTGCTGA GTTGTTATTT AAGCTTGCCC AAAAAGAAGA AGAGTCGAAT
  CTTAAGTTGA AGAGGTATGA AACCTATTCC TTTATGTCTG TACTTTTTAG AGTAACGACT CAACAATAAA TTCGAACGGG TTTTTCTTCT TCTCAGCTTA

                                                                                          sau3AI
           bspMI                                                                          mboI/ndeII[dam-]
        hinPI                                                                             dpnI[dam+]
        hhaI/cfoI                                                 hinPI         aciI      dpnII[dam-]
       mstI         aluI             mslI                         hhaI/cfoI    nspBII    bclI[dam-] mnlI
       aviII/fspI  hindIII          maeIII bsrDI
101 GAACTGTGTG CGCAGGTAGA AGCTTTGGAG ATTATCGTCA CTGCAATGCT TCGCAATATG GCGCAAAATG ACCAACAGCG GTTGATTGAT CAGGTAGAGG
    CTTGACACAC GCGTCCATCT TCGAAACCTC TAATAGCAGT GACGTTACGA AGCGTTATAC CGCGTTTTAC TGGTTGTCGC CAACTAACTA GTCCATCTCC

                                                            thaI
                                                            fnuDII/mvnI
                                                         fnu4HI
                                                         bsoFI
                                                         bbvI       maeII
                                                       fnu4HI bstUI  snaBI
     rsaI                                              bsoFI  bsh1236I
  hinPI                                                bbvI  hinPI   bsaAI                mnlI
  hhaI/cfoI mnlI               cac8I                  aluI  hhaI/cfoI                    fokI
 haeII csp6I               sfaNI   bsmI                                                  sfaNI
201 GGGCGCTGTA CGAGGTAAAG CCCGATGCCA GCATTCCTGA CGACGATACG GAGCTGCTGC GCGATTACGT AAAGAAGTTA TTGAAGCATC CTCGTCAGTA
    CCCGCGACAT GCTCCATTTC GGGCTACGGT CGTAAGGACT GCTGCTATGC CTCGACGACG CGCTAATGCA TTTCTTCAAT AACTTCGTAG GAGCAGTCAT

                                                                                                  aluI
                                                                                                  sstI
                                                                                                  sacI
                                                                                                  hgiJII
                                          haeIII/palI                                             hgiAI/aspHI
                                         mcrI                                                     ecl136II
                                         eagI/xmaIII/eclXI                                  ecoRI bsp1286
                                         eaeI                                            rmaI     bsiHKAI
                                         cfrI                                            maeI     bmyI
                   aluI                  bsiEI   ahdI/eam1105I               tru9I       bfaI    taqI
    tru9I          pvuII                maeIII    bsmAI                      mseI      maeIII  apoI  banII
    mseI           nspBII
301 AAAAGTTAAT CTTTTCAACA GCTGTCATAA AGTTGTCACG GCCGAGACTT ATAGTCGCTT TGTTTTTATT TTTTAATGTA TTTGTAACTA GAATTCGAGC
    TTTTCAATTA GAAAAGTTGT CGACAGTATT TCAACAGTGC CGGCTCTGAA TATCAGCGAA ACAAAAATAA AAAATTACAT AAACATTGAT CTTAAGCTCG
```

FIG. 41A

```
          scrFI
          nciI
          mspI
          hpaII
          dsaV
         xmaI/pspAI
         smaI
         scrFI
         nciI
         dsaV
         cauII        xhoI
         bsaJI       mnlI
         avaI     sau3AI taqI
      rsaI        mboI/ndeII[dam-]
      csp6I       dpnI[dam+]
     nlaIV       nlaIV  paeR7I
     kpnI cauII dpnII[dam-]
     hgiCI       bstYI/xhoII
     banI bsaJI alwI[dam-]
     asp718     bamHI  avaI        hphI
     acc65I     alwI[dam-] mnlI   mnlI                              mboII    sfaNI
401 TCGGTACCCG GGGATCCTCT CGAGGTTGAG GTGATTTTAT GAAAAAGAAT ATCGCATTTC TTCTTGCATC TATGTTCGTT TTTTCTATTG CTACAAACGC
    AGCCATGGGC CCCTAGGAGA GCTCCAACTC CACTAAAATA CTTTTTCTTA TAGCGTAAAG AAGAACGTAG ATACAAGCAA AAAAGATAAC GATGTTTGCG
                                               M   K   K   N   I   A   F   L   L   A   S   M   F   V   F   S   I   A   T   N   A
-23
      a mutation was found that inactivated the mluI site.  The penultimate nucleotide was changed fr G toT ^

                                      sstI
                                      sacI
                                      hgiJII
                                      hgiAI/aspHI
                                      ecl136II
                                      bsp1286
                                      bsiHKAI                                               bspMI
                                                                                          scfI
                                                                                          pstI
                                                                        hphI             sse8387I           ddeI    nlaIII
                                bsmFI bmyI                                               bspMI            aluI   rsaI
                             bsrI  avaI aluI              mnlI           maeIII                         hindIII csp6I
           ecoRV          tth111I/aspI  banII            aciI            bstEII  hphI bsgI
501 ATACGCTGAT ATCCAGATGA CCCAGTCCCC GAGCTCCCTG TCCGCCTCTG TGGGCGATAG GGTCACCATC ACCTGCAGGT CAAGTCAAAG CTTAGTACAT
    TATGCGACTA TAGGTCTACT GGGTCAGGGG CTCGAGGGAC AGGCGGAGAC ACCCGCTATC CCAGTGGTAG TGGACGTCCA GTTCAGTTTC GAATCATGTA
-2   Y   A   D   I   Q   M   T   Q   S   P   S   S   L   S   A   S   V   G   D   R   V   T   I   T   C   R   S   S   Q   S   L   V   H
```

FIG. 41B

```
                                              scrFI                                            tfiI
                                              mvaI                                       hinfI       bsmFI
                                              ecoRII                                   taqI    bpmI/gsuI[dcm-]
                                              dsaV                                         claI/bsp106  pleI
                                              bstNI     aluI                               bspDI[dam-]  hinfI
                            bsrI              apyI[dcm+]
601 GGTATAGGTG CTACGTATTT ACACTGGTAT CAACAGAAAC CAGGAAAAGC TCCGAAACTA CTGATTTACA AAGTATCCAA TCGATTCTCT GGAGTCCCTT
    CCATATCCAC GATGCATAAA TGTGACCATA GTTGTCTTTG GTCCTTTTCG AGGCTTTGAT GACTAAATGT TTCATAGGTT AGCTAAGAGA CCTCAGGGAA
 32 G  I  G  A   T  Y  L   H  W  Y   Q  Q  K  P   G  K  A   P  K  L   L  I  Y  K   V  S  N   R  F  S   G  V  P  S

                    mspI
                    hpaII
                    bslI
                   bsaWI
                 sau3AI
                 mboI/ndeII[dam-]
                 dpnI[dam+]
                 dpnII[dam-]                                     fnu4HI
                 alwI[dam-]                                      bsoFI
                nlaIV                                            bbvI
                bstYI/xhoII                                    scfI      mboII                             rsaI
                bamHI                                          pstI      bpuAI                             csp6I
                alwI[dam-]   bsmFI                             bsgI      bbsI                             scaI  nlaIII
701 CTCGCTTCTC TGGATCCGGT TCTGGGACGG ATTTCACTCT GACCATCAGC AGTCTGCAGC CAGAAGACTT CGCAACTTAT TACTGTTCAC AGAGTACTCA
    GAGCGAAGAG ACCTAGGCCA AGACCCTGCC TAAAGTGAGA CTGGTAGTCG TCAGACGTCG GTCTTCTGAA GCGTTGAATA ATGACAAGTG TCTCATGAGT
 66   R  F  S   G  S  G   S  G  T  D   F  T  L   T  I  S   S  L  Q  P   E  D  F   A  T  Y   Y  C  S  Q   S  T  H

                                 styI
                                 bsaJI
                              rsaI
                              csp6I
                             nlaIV
                             kpnI
                             hgiCI          sau3AI
        bsrBI                banI           mboI/ndeII[dam-]  fnu4HI         mboII
        aciI                 asp718         dpnI[dam+]        bsoFI         bpuAI        aciI
      bsmFI     maeII        acc65I         dpnII[dam-]       bbvI          bbsI    mboII
801 TGTCCCGCTC ACGTTTGGAC AGGGTACCAA GGTGGAGATC AAACGAACTG TGGCTGCACC ATCTGTCTTC ATCTTCCCGC CATCTGATGA GCAGTTGAAA
    ACAGGGCGAG TGCAAACCTG TCCCATGGTT CCACCTCTAG TTTGCTTGAC ACCGACGTGG TAGACAGAAG TAGAAGGGCG GTAGACTACT CGTCAACTTT
 99  V  P  L   T  F  G  Q   G  T  K   V  E  I   K  R  T  V   A  A  P   S  V  F   I  F  P  P   S  D  E   Q  L  K
```

FIG. 41C

```
                                                                                                              scrFI
                                                                                                              mvaI
                                                                                                              ecoRII
                                                                                                              dsaV
                                                                                                              bstNI
                                                        haeIII/palI                                          bsaJI
     xmnI                        xmnI                haeI       rsaI                      mnlI             maeIII apyI[dcm+]
     asp700             cac8I    asp700             mnlI        csp6I                     bslI
901  TCTGGAACTG CTTCTGTTGT GTGCCTGCTG AATAACTTCT ATCCCAGAGA GGCCAAAGTA CAGTGGAAGG TGGATAACGC CCTCCAATCG GGTAACTCCC
     AGACCTTGAC GAAGACAACA CACGGACGAC TTATTGAAGA TAGGGTCTCT CCGGTTTCAT GTCACCTTCC ACCTATTGCG GGAGGTTAGC CCATTGAGGG
132  S  G  T  A   S  V  V   C  L  L   N  N  F  Y   P  R  E   A  K  V   Q  W  K  V   D  N  A   L  Q  S   G  N  S  Q

                                                 fnu4HI
                                                 bsoFI          celII/espI
                                              ddeI              blpI/bpu1102I
        maeIII                       scfI   mnlI bbvI        hgaI ddeI                                 accI   cac8I
1001 AGGAGAGTGT CACAGAGCAG GACAGCAAGG ACAGCACCTA CAGCCTCAGC AGCACCCTGA CGCTGAGCAA AGCAGACTAC GAGAAACACA AAGTCTACGC
     TCCTCTCACA GTGTCTCGTC CTGTCGTTCC TGTCGTGGAT GTCGGAGTCG TCGTGGGACT GCGACTCGTT TCGTCTGATG CTCTTTGTGT TTCAGATGCG
166   E  S  V   T  E  Q   D  S  K  D   S  T  Y   S  L  S   S  T  L  T   L  S  K   A  D  Y   E  K  H  K   V  Y  A

                          cac8I
                         aluI
                        sstI
                        sacI
                        hgiJII
                        hgiAI/aspHI
                        ecl136II
                        bsp1286
                        bsiHKAI
                        bmyI                                                          mnlI                         rmaI
                    haeIII/palI                                                      sau3AI                        maeI
                   sau96I banII                                                      mboI/ndeII[dam-]              bfaI
                   asuI ddeI                                                  aluI   dpnI[dam+]      hgaI       sau96I
                  eco0109I/draII                                            tru9I    dpnII[dam-] mspI           haeIII/palI
       hphI      alwNI[dcm-]          maeIII    aluI                        mseI     alwI[dam-]  hpaII sfaNI    asuI
       maeIII
1101 CTGCGAAGTC ACCCATCAGG GCCTGAGCTC GCCCGTCACA AAGAGCTTCA ACAGGGGAGA GTGTTAAGCT GATCCTCTAC GCCGGACGCA TCGTGGCCCT
     GACGCTTCAG TGGGTAGTCC CGGACTCGAG CGGGCAGTGT TTCTCGAAGT TGTCCCCTCT CACAATTCGA CTAGGAGATG CGGCCTGCGT AGCACCGGGA
199   C  E  V   T  H  Q  G   L  S  S   P  V  T   K  S  F  N   R  G  E   C  O  (SEQ ID NO.56)
```

FIG. 41D

```
                 rmaI                         rmaI
                 maeI                         maeI
       rsaI      bfaI                         bfaI        hphI                                          mboII    sfaNI
       csp6I    speI                          xbaI mnlI  mnlI
1201 AGTACGCAAC TAGTCGTAAA AAGGGTATCT AGAGGTTGAG GTGATTTTAT GAAAAAGAAT ATCGCATTTC TTCTTGCATC TATGTTCGTT TTTTCTATTG
     TCATGCGTTG ATCAGCATTT TTCCCATAGA TCTCCAACTC CACTAAAATA CTTTTTCTTA TAGCGTAAAG AAGAACGTAG ATACAAGCAA AAAAGATAAC
                                                            M   K  K  N   I  A  F  L   L  A  S   M  F  V   F  S  I  A
-23

                                                                                 scrFI
                                                                                 mvaI
                                                                                 ecoRII
                                                                                 dsaV
                                                                      scrFI
            rsaI                                                      mvaI    fnu4HI
          bsiWI/splI                                                  ecoRII
        thaI                                                          dsaV bstNI hgiJII                aluI
        fnuDII/mvnI                                                   bstNI  bsoFI     bsp1286            alwNI[dcm-]
        bstUI                 rmaI                                    apyI[dcm+] bsaJI bmyI              fnu4HI
        bsh1236I              maeI                                  haeIII/palI  apyI[dcm+]              bsoFI
       mluI csp6I  mnlI       bfaI                             aciI haeI       bbvI        banII          bbvI
       aflIII     ddeI      aluI
1301 CTACAAACGC GTACGCTGAG GTTCAGCTAG TGCAGTCTGG CGGTGGCCTG GTGCAGCCAG GGGGCTCACT CCGTTTGTCC TGTGCAGCTT CTGGCTACTC
     GATGTTTGCG CATGCGACTC CAAGTCGATC ACGTCAGACC GCCACCGGAC CACGTCGGTC CCCCGAGTGA GGCAAACAGG ACACGTCGAA GACCGATGAG
-5    T  N  A   Y  A  E   V  Q  L  V   Q  S  G   G  G  L   V  Q  P  G   G  S  L   R  L  S   C  A  A  S   G  Y  S

                                                         scrFI
                                                         nciI
                                                         mspI
                                                         hpaII
                                                         dsaV
                                                         cauII
                                                         bslI
                                                        xmaI/pspAI
                                                        smaI
                                                        scrFI
                                                        nciI
                                                        dsaV        scrFI
                                                        cauII       mvaI
                                                        bslI        ecoRII
```

FIG. 41E

```
                                 bsaJI           dsaV
                                 avaI            bstNI
                                 bsaJI           bslI                               bslI
        pleI                     sau96I          apyI[dcm+]                      sau3AI
        hinfI            sau96I  nlaIV        sau96I                  mboI/ndeII[dam-]                    maeII
       taqI              avaII   haeIII/palI  asuI                       dpnI[dam+]          snaBI
      xhoI               asuI    asuI        eco0109I/draII        dpnII[dam-]          hphI      bsaAI
      paeR7I             nlaIV   eco0109I/draII haeIII/palI           alwI[dam-]
      avaI maeIII      bsrI
1401 CTTCTCGAGT CACTATATGC ACTGGGTCCG TCAGGCCCCG GGTAAGGGCC TGGAATGGGT TGGATATATT GATCCTTCCA ATGGTGAAAC TACGTATAAT
     GAAGAGCTCA GTGATATACG TGACCCAGGC AGTCCGGGGC CCATTCCCGG ACCTTACCCA ACCTATATAA CTAGGAAGGT TACCACTTTG ATGCATATTA
  29  F  S  S   H  Y  M  H   W  V  R   Q  A  P   G  K  G  L   E  W  V   G  Y  I   D  P  S  N   G  E  T   T  Y  N

                                  thaI
                                  fnuDII/mvnI                 scfI
               haeIII/palI        bstUI                       pstI             cac8I    mnlI
              sau96I              bsh1236I                    bsgI            cac8I    ddeI  drdI
              asuI               nruI                        bspMI
1501 CAAAAGTTCA AGGGCCGTTT CACTTTATCT CGCGACAACT CCAAAAACAC AGCATACCTG CAGATGAACA GCCTGCGTGC TGAGGACACT GCCGTCTATT
     GTTTTCAAGT TCCCGGCAAA GTGAAATAGA GCGCTGTTGA GGTTTTTGTG TCGTATGGAC GTCTACTTGT CGGACGCACG ACTCCTGTGA CGGCAGATAA
  62 Q  K  F  K   G  R  F   T  L  S   R  D  N  S   K  N  T   A  Y  L   Q  M  N  S   L  R  A   E  D  T   A  V  Y  Y

                                                                                                  sau96I
                                                                                                  haeIII/palI
                                                                                                 sau96I
                                                                                                 nlaIV
                                                                                                 hgiJII
                                                                                                 bsp1286
                                                                  maeIII                         bsp120I
                                                                 bstEII                      bmyI
                                                               scrFI                             banII
                                                               mvaI            mnlI
                                                               ecoRII    bsaJI               asuI
                                            maeII              dsaV     bseRI                apaI
                                           hinlI/acyI          bstNI      esp3I                styI asuI
                                           ahaII/bsaHI        bsaJI hphI bsmBI          mnlI   bsaJI
                           maeIII        taqI                                       haeIII/palI eco0109I/draII
                 mnlI     hphI bsrI  mboII aatII        nlaIV apyI[dcm+] bsmAI
1601 ACTGTGCAAG AGGGGATTAT CGCTACAATG GTGACTGGTT CTTCGACGTC TGGGGTCAAG GAACCCTGGT CACCGTCTCC TCGGCCTCCA CCAAGGGCCC
     TGACACGTTC TCCCCTAATA GCGATGTTAC CACTGACCAA GAAGCTGCAG ACCCCAGTTC CTTGGGACCA GTGGCAGAGG AGCCGGAGGT GGTTCCCGGG
  96  C  A  R   G  D  Y   R  Y  N  G   D  W  F   F  D  V   W  G  Q  G   T  L  V   T  V  S   S  A  S  T   K  G  P
                                                                  seq right is from p6G425chim2.fab2   ^
```

FIG. 41F

```
                                                                                     scrFI
                                                                                     mvaI
                                                                           scrFI
                                                                           mvaI      ecoRII
                                                                           ecoRII
                  nlaIV                                                    dsaV
                  hgiCI                                                    bstNI     ecoNI
                  banI                                             sau96I dsaV
               scrFI                                                    haeIII/palI  bstNI                    hphI
               mvaI                                                fnu4HI    fnu4HI                   mspI
               ecoRII                                              bsoFI bsaJI     bslI               hpaII
               dsaV              hgiAI/aspHI                             aciI  apyI[dcm+]                  cfr10I/bsrFI
      mboII    bstNI       bseRI       bsp1286                     bsp1286   asuI      bsoFI               bsaWI  tth111I/aspI
     bpuAI     apyI[dcm+]  mnlI        bsiHKAI                                                          bslI  ageI maeIII
     bbsI     bsaJI      mnlI          bmyI mnlI                   bmyI nspBII bsaJI bbvI apyI[dcm+]
1701 ATCGGTCTTC CCCCTGGCAC CCTCCTCCAA GAGCACCTCT GGGGGCACAG CGGCCCTGGG CTGCCTGGTC AAGGACTACT TCCCCGAACC GGTGACGGTG
     TAGCCAGAAG GGGGACCGTG GGAGGAGGTT CTCGTGGAGA CCCCCGTGTC GCCGGGACCC GACGGACCAG TTCCTGATGA AGGGGCTTGG CCACTGCCAC
 129 S  V  F   P  L  A  P   S  S  K   S  T  S   G  G  T  A   A  L  G   C  L  V   K  D  Y  F   P  E  P   V  T  V

                hinPI
                hhaI/cfoI
               nlaIV                      hgiAI/aspHI
               narI                       bsp1286
               kasI                       bsiHKAI         mspI
               hinlI/acyI            cac8I                 hpaII
               hgiCI              fnu4HI                  scrFI                ddeI                     fnu4HI
               haeII              bsoFI bmyI              nciI               mnlI   pleI                bsoFI    maeIII      mnlI
               banI               aciI  apaLI/snoI        dsaV               eco81I hinfI         ddeI          hphI       bsp1286
          ddeI ahaII/bsaHI nspBII alw44I/snoI cauII             scfI         bsu36I/mstII/sauI mnlI bbvI    bstEII     bmyI bpmI/gsuI[dcm-]
1801 TCGTGGAACT CAGGCGCCCT GACCAGCGGC GTGCACACCT TCCCGGCTGT CCTACAGTCC TCAGGACTCT ACTCCCTCAG CAGCGTGGTG ACCGTGCCCT
     AGCACCTTGA GTCCGCGGGA CTGGTCGCCG CACGTGTGGA AGGGCCGACA GGATGTCAGG AGTCCTGAGA TGAGGGAGTC GTCGCACCAC TGGCACGGGA
 162 S  W  N  S   G  A  L   T  S  G   V  H  T  F   P  A  V   L  Q  S   S  G  L  Y   S  L  S   S  V  V   T  V  P  S

        aluI    nlaIV                                                           taqI              hgiJII
       fnu4HI   hgiCI                                                          salI               bsp1286
       bsoFI    banI                         tfiI                        styI  hincII/hindII      bmyI
       bbvI    bsp1286                       hinfI                       bsaJI accI               banII          maeIII
     bstXI     bmyI                       maeII
1901 CCAGCAGCTT GGGCACCCAG ACCTACATCT GCAACGTGAA TCACAAGCCC AGCAACACCA AGGTCGACAA GAAAGTTGAG CCCAAATCTT GTGACAAAAC
     GGTCGTCGAA CCCGTGGGTC TGGATGTAGA CGTTGCACTT AGTGTTCGGG TCGTTGTGGT TCCAGCTGTT CTTTCAACTC GGGTTTAGAA CACTGTTTTG
 196  S  S  L   G  T  Q   T  Y  I  C   N  V  N   H  K  P   S  N  T  K   V  D  K   K  V  E   P  K  S  C   D  K  T
```

FIG. 41G

```
                                    fnu4HI
                                     bsoFI
                                    haeIII/palI
                                   mcrI
                                   eagI/xmaIII/eclXI
                                   eaeI
                                   cfrI
                                   bsiEI                                   sapI
         cac8I                     notI               rmaI                 mboII                  rmaI
       nlaIII                      fnu4HI             maeI                 earI/ksp632I           maeI
      nspI        bsp1286          bsoFI    nlaIII    bfaI     tth111I/aspI                       bfaI
      nspHI   aciI bmyI            aciI aciI         aluI mnlI      taqI    aluI
2001 TCACACATGC CCGCCGTGCC CAGCACCAGA ACTGCTGGGC GGCCGCATGA AACAGCTAGA GGACAAGGTC GAAGAGCTAC TCTCCAAGAA CTACCACCTA
     AGTGTGTACG GGCGGCACGG GTCGTGGTCT TGACGACCCG CCGGCGTACT TTGTCGATCT CCTGTTCCAG CTTCTCGATG AGAGGTTCTT GATGGTGGAT
229  H  T  C   P  P  C  P   A  P  E   L  L  G   G  R  M  K   Q  L  E   D  K  V   E  E  L  L   S  K  N   Y  H  L
       ^junction between antibody and leucine zipper

                                                                                            scrFI
                                       sphI                                                 nciI
                                    ddeI nlaIII                                             mspI
                                   celII/espI          rmaI                                 hpaII
                                   blpI/bpu1102I       maeI                                 dsaV
                                 hinPI    nspI         bfaI   bsmFI                         cauII
                                 hhaI/cfoI           sau96I  pleI                         aciI
            pleI       aluI     haeII    nspHI       haeIII/palI                         fnu4HI
            hinfI      hindIII  eco47III cac8I       asuI    hinfI                        bsoFI
2101 GAGAATGAAG TGGCAAGACT CAAAAAGCTT GTCGGGGAGC GCTAAGCATG CGACGGCCCT AGAGTCCCTA ACGCTCGGTT GCCGCCGGGC GTTTTTTATT
     CTCTTACTTC ACCGTTCTGA GTTTTTCGAA CAGCCCCTCG CGATTCGTAC GCTGCCGGGA TCTCAGGGAT TGCGAGCCAA CGGCGGCCCG CAAAAAATAA
262  E  N  E  V   A  R  L   K  K  L   V  G  E  R   O (SEQ ID NO.60)

                             aluI
     tru9I              taqI  hindIII                                          nlaIV
     mseI             claI/bsp106 tru9I                    tru9I               hgiCI
     hpaI  nlaIII     bspDI[dam-] mseI   aciI              mseI                banI
     hincII/hindII  aluI
2201 GTTAACTCAT GTTTGACAGC TTATCATCGA TAAGCTTTAA TGCGGTAGTT TATCACAGTT AAATTGCTAA CGCAGTCAGG CACCGTGTAT GAAATCTAAC
     CAATTGAGTA CAAACTGTCG AATAGTAGCT ATTCGAAATT ACGCCATCAA ATAGTGTCAA TTTAACGATT GCGTCAGTCC GTGGCACATA CTTTAGATTG
```

FIG. 41H

```
                                         sfaNI                                                          haeIII/palI
                                      scrFI                                                     sau96I
                                      mvaI                                                          scrFI
                                      ecoRII                                               nciI
                                      dsaV                                          rsaI   mspI mnlI
                             nlaIV    bstNI                                               csp6I  hpaII
                         mnlI hgiCI  bsaJI                                            mspI       dsaV bslI
     hinPI               bsaJI      hphI apyI[dcm+]                                    hpaII      cauII         ecoRV
     hhaI/cfoI    fokI      banI   maeIII    fokI   scfI                               cfr10I/bsrFI asuI     aciI
2301 AATGCGCTCA TCGTCATCCT CGGCACCGTC ACCCTGGATG CTGTAGGCAT AGGCTTGGTT ATGCCGGTAC TGCCGGGCCT CTTGCGGGAT ATCGTCCATT
     TTACGCGAGT AGCAGTAGGA GCCGTGGCAG TGGGACCTAC GACATCCGTA TCCGAACCAA TACGGCCATG ACGGCCCGGA GAACGCCCTA TAGCAGGTAA

                                        hinPI
                                        hhaI/cfoI
                                      rmaI
                                      maeI
                                     nheI
                                 fnu4HI haeII                                                                fnu4HI
                                 bsoFI   eco47III                            hinPI          hgiAI/aspHI      bsoFI
                                 bbvI bfaI                                   hhaI/cfoI      bsp1286    aciI  haeIII/palI
                       maeIII                                               mstI  bslI      bsiHKAI  mcrI    eaeI
        sfaNI   bsrI        cac8I    cac8I              sfaNI              aviII/fspI      bmyI     bsiEI   cfrI
2401 CCGACAGCAT CGCCAGTCAC TATGGCGTGC TGCTAGCGCT ATATGCGTTG ATGCAATTTC TATGCGCACC CGTTCTCGGA GCACTGTCCG ACCGCTTTGG
     GGCTGTCGTA GCGGTCAGTG ATACCGCACG ACGATCGCGA TATACGCAAC TACGTTAAAG ATACGCGTGG GCAAGAGCCT CGTGACAGGC TGGCGAAACC

                                                                                   mnlI
                                                                                 sau3AI
                                                       sau3AI                    mboI/ndeII[dam-]
                                                       mboI/ndeII[dam-]          dpnI[dam+]
                                                       dpnI[dam+]                dpnII[dam-]
                                                       dpnII[dam-]               alwI[dam-]
                                                    thaI                         nlaIV
       aciI                                         fnuDII/mvnI                  bstYI/xhoII      hgaI
      fnu4HI                                        bstUI  nlaIII                bamHI         mspI
      bsoFI                                         bsh1236I          bslI       alwI[dam-]    hpaII  sfaNI
     aciI    bsrI      cac8I          nlaIV      taqI
2501 CCGCCGCCCA GTCCTGCTCG CTTCGCTACT TGGAGCCACT ATCGACTACG CGATCATGGC GACCACACCC GTCCTGTGGA TCCTCTACGC CGGACGCATC
     GGCGGCGGGT CAGGACGAGC GAAGCGATGA ACCTCGGTGA TAGCTGATGC GCTAGTACCG CTGGTGTGGG CAGGACACCT AGGAGATGCG GCCTGCGTAG
```

FIG. 41I

```
                                hinPI
                                hhaI/cfoI
                               nlaIV
                               narI
                               kasI                          hinPI
                               hinlI/acyI                    hhaI/cfoI
               mspI            hgiCI                        nlaIV
               hpaII           haeII                        narI
              naeI          mspI                            kasI
              cfr10I/bsrFI banI                             hinlI/acyI
              cac8I     sgrAI                               hgiCI
             haeIII/palI hpaII                              haeII
            eaeI      hphI ahaII/bsaHI                      banI
            cfrI  sfaNI cfr10I/bsrFI    aciI   cac8I        ahaII/bsaHI
2601 GTGGCCGGCA TCACCGGCGC CACAGGTGCG GTTGCTGGCG CCTATATCGC
     CACCGGCCGT AGTGGCCGCG GTGTCCACGC CAACGACCGC GGATATAGCG

                                   hgiJII
                                   bsp1286
                                   bmyI
                                   banII
                              sau3AI cac8I                    rcaI   hinPI
                              mboI/ndeII[dam-]     hgiJII     haeII
                              dpnI[dam+]           bsp1286    eco47III
                              dpnII[dam-]          bmyI bspHI hhaI/cfoI
           hphI            mboII[dam-]             banII nlaIII
     CGACATCACC GATGGGGAAG ATCGGGCTCG CCACTTCGGG CTCATGAGCG
     GCTGTAGTGG CTACCCCTTC TAGCCCGAGC GGTGAAGCCC GAGTACTCGC

                                 scrFI
                                 nciI
                                 mspI
                                 hpaII
                            dsaI dsaV
                            bslI cauII
                       sau96I haeIII/palI
                       nlaIV   eaeI
                       haeIII/palI
                       asuI bsaJI bsaJI
                      eco0109I/draII
                    cac8I bslI cfrI    bsmFI
2701 CTTGTTTCGG CGTGGGTATG GTGGCAGGCC CCGTGGCCGG GGGACTGTTG
     GAACAAAGCC GCACCCATAC CACCGTCCGG GGCACCGGCC CCCTGACAAC

                                                fnu4HI
      hinPI                                     bsoFI hgiAI/aspHI
      hhaI/cfoI                                 aciI  bsp1286
     nlaIV                                   fnu4HI   bsiHKAI
     narI                                    bsoFI    bmyI
     kasI                                    
     hinlI/acyI
     hgiCI
     haeII
     banI
     ahaII/bsaHI    cac8I          bslI      aciI  aciI          haeIII/palI
     GGCGCCATCT CCTTGCACGC ACCATTCCTT GCGGCGGCGG TGCTCAACGG
     CCGCGGTAGA GGAACGTGCG TGGTAAGGAA CGCCGCCGCC ACGAGTTGCC

                       fnu4HI
                       bsoFI   ecoNI       pleI
     mnlI  bslI   bsrI bbvI    bslI        hinfI
2801 CCTCAACCTA CTACTGGGCT GCTTCCTAAT GCAGGAGTCG CATAAGGGAG
     GGAGTTGGAT GATGACCCGA CGAAGGATTA CGTCCTCAGC GTATTCCCTC

                                                     mspI
                                                     hpaII
                                                    bsaWI
       hgaI        sfaNI                   bsrI  aluI bslI
     AGCGTCGTCC GATGCCCTTG AGAGCCTTCA ACCCAGTCAG CTCCTTCCGG
     TCGCAGCAGG CTACGGGAAC TCTCGGAAGT TGGGTCAGTC GAGGAAGGCC
```

FIG. 41J

```
                                                                                                   fnu4HI
                                                                                                mspI  hinPI
       aciI                                                                                    naeI  haeII
      thaI                                                                                     cfr10I/bsrFI
      fnuDII/mvnI                                                                              cac8I  eco47III
      bstUI    nlaIII                                                                      nlaIV    bsoFI
      bsh1236I                     aciI              mboII                                 hgiCI    bbvI
     hinPI    bcgI                fnu4HI           bpuAI                                   banI  hpaII  hhaI/cfoI               mnlI
     hhaI/cfoI                    bsoFI            bbsI          nlaIII
2901 TGGGCGCGGG GCATGACTAT CGTCGCCGCA CTTATGACTG TCTTCTTTAT CATGCAACTC GTAGGACAGG TGCCGGCAGC GCTCTGGGTC ATTTTCGGCG
     ACCCGCGCCC CGTACTGATA GCAGCGGCGT GAATACTGAC AGAAGAAATA GTACGTTGAG CATCCTGTCC ACGGCCGTCG CGAGACCCAG TAAAAGCCGC

                         thaI                                                                                     sau96I
                         fnuDII/mvnI                                                                              nlaIV
                         bstUI         haeIII/palI                                                                avaII
       aciI              bsh1236I   sau3AI                                                                        asuI
     sau96I             hinPI       mboI/ndeII[dam-]                                                           bsrI     aciI
     avaII              hhaI/cfoI   dpnI[dam+]          aciI           tfiI                                 maeIII    bsmFI
     asuI          bpmI/gsuI[dcm-]  dpnII[dam-]        cac8I           hinfI     cac8I  mnlI
3001 AGGACCGCTT TCGCTGGAGC GCGACGATGA TCGGCCTGTC GCTTGCGGTA TTCGGAATCT TGCACGCCCT CGCTCAAGCC TTCGTCACTG GTCCCGCCAC
     TCCTGGCGAA AGCGACCTCG CGCTGCTACT AGCCGGACAG CGAACGCCAT AAGCCTTAGA ACGTGCGGGA GCGAGTTCGG AAGCAGTGAC CAGGGCGGTG

                                               mcrI
                                               eagI/xmaIII/eclXI
                                               eaeI     hinPI
                                               cfrI     hhaI/cfoI                                         thaI
                                     mspI      bsiEI   thaI                                             hgaI
                                    naeI       fnu4HI  fnuDII/mvnI                                   thaI  fnuDII/mvnI
                                    cfr10I/bsrFI       bstUI                                          fnuDII/mvnI
                        haeIII/palI hpaII      bsoFI   bsh1236I                                       bstUI  bstUI
     maeII              haeI        cac8I      aciI  hgaI                                             bsh1236I  mnlI      haeI
     psp1406I        cac8I          bglI  nlaIII  haeIII/palI        maeII     cac8I      nruI     bsh1236I  fokI  haeIII/palI
3101 CAAACGTTTC GGCGAGAAGC AGGCCATTAT CGCCGGCATG GCGGCCGACG CGCTGGGCTA CGTCTTGCTG GCGTTCGCGA CGCGAGGCTG GATGGCCTTC
     GTTTGCAAAG CCGCTCTTCG TCCGGTAATA GCGGCCGTAC CGCCGGCTGC GCGACCCGAT GCAGAACGAC CGCAAGCGCT GCGCTCCGAC CTACCGGAAG
```

FIG. 41K

```
                                                                        bspMI
                                                  thaI                scrFI
                                   fnu4HI         fnuDII/mvnI         mvaI
                                   bsoFI          bstUI               ecoRII
                                   aciI        cac8I      haeI        dsaV
         mboII                   mspI   mslI  sfaNI bsh1236I haeIII/palI bstNI
      tfiI                       hpaII sfaNI fokI  aciI  cac8I nlaIII apyI[dcm+]              bsmFI aluI   alwI[dam-]
      hinfI
3201 CCCATTATGA TTCTTCTCGC TTCCGGCGGC ATCGGGATGC CCGCGTTGCA GGCCATGCTG TCCAGGCAGG TAGATGACGA CCATCAGGGA CAGCTTCAAG
     GGGTAATACT AAGAAGAGCG AAGGCCGCCG TAGCCCTACG GGCGCAACGT CCGGTACGAC AGGTCCGTCC ATCTACTGCT GGTAGTCCCT GTCGAAGTTC

       fnu4HI
       bsoFI
       aciI
      thaI                                sau96I
      fnuDII/mvnI                         avaII
      bstUI                            bsrI       sau3AI                      mnlI
    cac8I                           sau3AI asuI   mboI/ndeII[dam-]            bsaJI    hgiAI/aspHI
  sau3AI bsh1236I                   mboI/ndeII[dam-]                        aciI       bsp1286
  mboI/ndeII[dam-]                  dpnI[dam+] nspBII    maeIII            fnu4HI      bsiHKAI
  dpnI[dam+]                        dpnII[dam-]       dpnI[dam+]           bsoFI       bmyI
  dpnII[dam-]                     taqI[dam-]    aciI dpnII[dam-]           bglI     cac8I  nlaIII        nlaIII
3301 GATCGCTCGC GGCTCTTACC AGCCTAACTT CGATCACTGG ACCGCTGATC GTCACGGCGA TTTATGCCGC CTCGGCGAGC ACATGGAACG GGTTGGCATG
     CTAGCGAGCG CCGAGAATGG TCGGATTGAA GCTAGTGACC TGGCGACTAG CAGTGCCGCT AAATACGGCG GAGCCGCTCG TGTACCTTGC CCAACCGTAC

        fnu4HI
        bsoFI
      hinPI                                                        haeIII/palI
      hhaI/cfoI                                                   sau96I                      fnu4HI
     nlaIV                                                       scrFI                        bsoFI
     narI                                         thaI           nciI                         aciI
     kasI                               thaI      fnuDII/mvnI    mspI                       mspI     mnlI
     hinlI/acyI                         fnuDII/mvnI              hpaII                      hpaII nlaIV
     hgiCI                              bstUI     bstUI          dsaV                      naeI   hgiCI
     haeII                              bsh1236I  bsh1236I nlaIV  asuI     taqI            cfr10I/bsrFI
     banI aciI                        mnlI aciI  hgaI aciI  nlaIII cauII  mnlI             cac8I  banI
     ahaII/bsaHI
3401 GATTGTAGGC GCCGCCCTAT ACCTTGTCTG CCTCCCCGCG TTGCGTCGCG GTGCATGGAG CCGGGCCACC TCGACCTGAA TGGAAGCCGG CGGCACCTCG
     CTAACATCCG CGGCGGGATA TGGAACAGAC GGAGGGGCGC AACGCAGCGC CACGTACCTC GGCCCGGTGG AGCTGGACTT ACCTTCGGCC GCCGTGGAGC
```

FIG. 41L

```
                                                                          hinPI                                       hgaI
                                                                          hhaI/cfoI                                   thaI aciI
                                                                         mstI     pflMI                               fnuDII/mvnI
     hphI                                                                aviII/fspI      styI                         bstUI
    tfiI        pflMI                                                                                                 bsh1236I
    hinfI       bslI      nlaIV                   aciI            bsmI            bslI   bsaJI
3501 CTAACGGATT CACCACTCCA AGAATTGGAG CCAATCAATT CTTGCGGAGA ACTGTGAATG CGCAAACCAA CCCTTGGCAG AACATATCCA TCGCGTCCGC
     GATTGCCTAA GTGGTGAGGT TCTTAACCTC GGTTAGTTAA GAACGCCTCT TGACACTTAC GCGTTTGGTT GGGAACCGTC TTGTATAGGT AGCGCAGGCG

                                                 haeIII/palI
                                                mscI/balI
                                                haeI
                                               scrFI                                                     mspI
                                               mvaI dsaI                                              hpaII
                                               ecoRII                                                 scrFI
                                               dsaV                                                      nciI
                                               bstNI                                                     dsaV
            fnu4HI                             bslI bsaJI           sau3AI                              sau96I
           thaI hinPI                          apyI[dcm+]           mboI/ndeII[dam-]
       fnu4HI bsoFI                           sau96I           dpnI[dam+]                        nlaIV
       bsoFI fnuDII/mvnI                      avaII      hinPI dpnII[dam-]                       avaII       cac8I
    fnu4HI     bstUI                          asuI eaeI  hhaI/cfoI  hgiAI/aspHI                  asuI     rmaI
    bsoFI   cac8I    hhaI/cfoI    fnu4HI     ppuMI      mstI nlaIII bsp1286                     ppuMI     maeI
    bbvI aciI bsh1236I    avaI    bsoFI      nlaIV cfrI       aviII/fspI  bsiHKAI                   eco0109I/draII
  bpmI/gsuI[dcm-] aciI  sfaNI     bbvI       eco0109I/draII   mslI    bmyI                 mnlI cauII-bfaI    aciI
3601 CATCTCCAGC AGCCGCACGC GGCGCATCTC GGGCAGCGTT GGGTCCTGGC CACGGGTGCG CATGATCGTG CTCCTGTCGT TGAGGACCCG GCTAGGCTGG
     GTAGAGGTCG TCGGCGTGCG CCGCGTAGAG CCCGTCGCAA CCCAGGACCG GTGCCCACGC GTACTAGCAC GAGGACAGCA ACTCCTGGGC CGATCCGACC

                                                                           fnu4HI
                                                                           bsoFI
                                                 cac8I                     bbvI
                                                thaI                     fnu4HI
                                   hphI         fnuDII/mvnI              bsoFI
                                tfiI            bstUI                    bbvI        maeII      ddeI        nlaIII
                  bsrI          hinfI           bsh1236I  maeII
3701 CGGGGTTGCC TTACTGGTTA GCAGAATGAA TCACCGATAC GCGAGCGAAC GTGAAGCGAC TGCTGCTGCA AAACGTCTGC GACCTGAGCA ACAACATGAA
     GCCCCAACGG AATGACCAAT CGTCTTACTT AGTGGCTATG CGCTCGCTTG CACTTCGCTG ACGACGACGT TTTGCAGACG CTGGACTCGT TGTTGTACTT
```

FIG. 41M

```
                                                                                  sau3AI
                                                                                  mboI/ndeII[dam-]
                                                                                  mamI[dam-]
                                                                                  dpnI[dam+]
                                                                                  dpnII[dam-]
                                                                                bstYI/xhoII
                                                                                alwI[dam-]
                                                                              mspI
                                                                              hpaII
                                             aciI                            mroI bsaBI[dam-]        fnu4HI
                                            thaI                             bspMII                  bsoFI
        mboII                               fnuDII/mvnI hinPI                bspEI[dam-]             bbvI
       bpuAI                                bstUI      hhaI/cfoI             bsaWI      sfaNI    sfaNI
       bbsI                                 bsh1236I   haeII     mslI        accIII[dam-]       fokI    cac8I
3801 TGGTCTTCGG TTTCCGTGTT TCGTAAAGTC TGGAAACGCG GAAGTCAGCG CCCTGCACCA TTATGTTCCG GATCTGCATC GCAGGATGCT GCTGGCTACC
     ACCAGAAGCC AAAGGCACAA AGCATTTCAG ACCTTTGCGC CTTCAGTCGC GGGACGTGGT AATACAAGGC CTAGACGTAG CGTCCTACGA CGACCGATGG

                                                                              aciI
                                        cac8I                              bsmFI     fokI
                                      hinPI                               sau96I     sfaNI
                                      hhaI/cfoI                           nlaIV  aciI
                             tru9I  haeII                                 avaII  fnu4HI          bsrI
                             mseI   eco47III          ddeI                asuI   bsoFI         aciI           mnlI
3901 CTGTGGAACA CCTACATCTG TATTAACGAA GCGCTGGCAT TGACCCTGAG TGATTTTTCT CTGGTCCCGC CGCATCCATA CCGCCAGTTG TTTACCCTCA
     GACACCTTGT GGATGTAGAC ATAATTGCTT CGCGACCGTA ACTGGGACTC ACTAAAAAGA GACCAGGGCG GCGTAGGTAT GGCGGTCAAC AAATGGGAGT

                         nspI
                     scrFI
                     nciI
                     mspI
             bsrI    hpaII
             bslI    dsaV nlaIII                                     mnlI
        maeII        cauII                                        fokI
       psp1406I  maeIII  nspHI            maeIII                sfaNI                                 nlaIII     apoI   bslI
4001 CAACGTTCCA GTAACCGGGC ATGTTCATCA TCAGTAACCC GTATCGTGAG CATCCTCTCT CGTTTCATCG GTATCATTAC CCCCATGAAC AGAAATTCCC
     GTTGCAAGGT CATTGGCCCG TACAAGTAGT AGTCATTGGG CATAGCACTC GTAGGAGAGA GCAAAGTAGC CATAGTAATG GGGGTACTTG TCTTTAAGGG
```

FIG. 41N

```
                                                                      cac8I
                                                                     sau96I
                                                           tru9I     haeIII/palI                        tru9I
                                                           mseI      asuI                               mseI      bpmI/gsuI[dcm-]
                     sfaNI                             aciI bslI  nlaIII aciI
                 mnlI          maeIII
4101 CCTTACACGG AGGCATCAAG TGACCAAACA GGAAAAAACC GCCCTTAACA TGGCCCGCTT TATCAGAAGC CAGACATTAA CGCTTCTGGA GAAACTCAAC
     GGAATGTGCC TCCGTAGTTC ACTGGTTTGT CCTTTTTTGG CGGGAATTGT ACCGGGCGAA ATAGTCTTCG GTCTGTAATT GCGAAGACCT CTTTGAGTTG

                                                                                    fnu4HI   thaI
                                                                                    bsoFI    fnuDII/mvnI
                                                                                   aluI      bstUI
                                                                                  pvuII     hinPI
                                                                                  nspBII    hhaI/cfoI
         aciI                                                                    fnu4HI    thaI
        thaI                                                                     bsoFI     fnuDII/mvnI
        fnuDII/mvnI                  xmnI                                        bcgI      bstUI
        bstUI                        tfiI                                        bbvI    mnlI bsh1236I
        bsh1236I                     hinfI                                      aciI  bbvI  bsh1236I  hphI      hphI
   aluI hgaI  fokI                   asp700          mslI        aluI
4201 GAGCTGGACG CGGATGAACA GGCAGACATC TGTGAATCGC TTCACGACCA CGCTGATGAG CTTTACCGCA GCTGCCTCGC GCGTTTCGGT GATGACGGTG
     CTCGACCTGC GCCTACTTGT CCGTCTGTAG ACACTTAGCG AAGTGCTGGT GCGACTACTC GAAATGGCGT CGACGGAGCG CGCAAAGCCA CTACTGCCAC

                          esp3I
                          bsmBI
                          bsmAI
                        mspI                                                                   hgaI
                  fnu4HI  hpaII                                scrFI                           thaI
                  bsoFI  scrFI                                 nciI                            fnuDII/mvnI
                  bbvI   nciI                                  mspI                            bstUI  aciI
                nlaIII   dsaV                                  hpaII                           bsh1236I
               nspI      cauII                              sfaNI                             hinPI nspBII
         mnlI  nspHI aluI bslI        maeIII   aluI        fokI dsaV                          hhaI/cfoI          aciI
                                                          aciI  cauII     drdI
4301 AAAACCTCTG ACACATGCAG CTCCCGGAGA CGGTCACAGC TTGTCTGTAA GCGGATGCCG GGAGCAGACA AGCCCGTCAG GGCGCGTCAG CGGGTGTTGG
     TTTTGGAGAC TGTGTACGTC GAGGGCCTCT GCCAGTGTCG AACAGACATT CGCCTACGGC CCTCGTCTGT TCGGGCAGTC CCGCGCAGTC GCCCACAACC
```

FIG. 41O

```
                fnu4HI                                                        sfaNI
                bsoFI            maeII                                       fnu4HI                       hgiAI/aspHI
                bbvI            maeIII                    bst1107I  tru9I    bsoFI               ddeI     bsp1286
              hinPI  nlaIII bsrI bsaAI                                       aciI                rsaI     bsiHKAI
              hhaI/cfoI  tth111I/aspI          aciI       accI bsrI mseI                         csp6I    bmyI  ndeI
                                                                                                          apaLI/snoI
                                                                                                          alw44I/snoI
4401 CGGGTGTCGG GGCGCAGCCA TGACCCAGTC ACGTAGCGAT AGCGGAGTGT ATACTGGCTT AACTATGCGG CATCAGAGCA GATTGTACTG AGAGTGCACC
     GCCCACAGCC CCGCGTCGGT ACTGGGTCAG TGCATCGCTA TCGCCTCACA TATGACCGAA TTGATACGCC GTAGTCTCGT CTAACATGAC TCTCACGTGG

                                                                     mboII
                                                                    earI/ksp632I                       hinPI
                                                                   sapI                                hhaI/cfoI
                                                                  hinPI                              fnu4HI
                                                            sfaNI hhaI/cfoI                  pleI    bsoFI    mcrI
       aciI         aciI   sfaNI                          aciI    haeII    aciI  mnlI        hinfI   bbvI     bsiEI
4501 ATATGCGGTG TGAAATACCG CACAGATGCG TAAGGAGAAA ATACCGCATC AGGCGCTCTT CCGCTTCCTC GCTCACTGAC TCGCTGCGCT CGGTCGTTCG
     TATACGCCAC ACTTTATGGC GTGTCTACGC ATTCCTCTTT TATGGCGTAG TCCGCGAGAA GGCGAAGGAG CGAGTGACTG AGCGACGCGA GCCAGCAAGC

     fnu4HI
     bsoFI
     aciI                                                                                  nlaIII          bslI
     fnu4HI      aciI                                                                      nspI            cac8I
     bsoFI    bsrBI                                              tfiI                      nspHI           haeIII/palI
     bbvI   cac8I     aluI          aciI                         hinfI                     aflIII          haeI
4601 GCTGCGGCGA GCGGTATCAG CTCACTCAAA GGCGGTAATA CGGTTATCCA CAGAATCAGG GGATAACGCA GGAAAGAACA TGTGAGCAAA AGGCCAGCAA
     CGACGCCGCT CGCCATAGTC GAGTGAGTTT CCGCCATTAT GCCAATAGGT GTCTTAGTCC CCTATTGCGT CCTTTCTTGT ACACTCGTTT TCCGGTCGTT

       scrFI          thaI
       mvaI                 fnuDII/mvnI
       ecoRII         bstUI
       dsaV           bsh1236I
       bstNI   bslI       aciI                                                          hgaI
       apyI[dcm+]        fnu4HI                                                         drdI
      haeIII/palI        bsoFI  cac8I                   aciI                           taqI             mnlI
     haeI  nlaIV       haeIII/palI                  nlaIV                 sfaNI
4701 AAGGCCAGGA ACCGTAAAAA GGCCGCGTTG CTGGCGTTTT TCCATAGGCT CCGCCCCCCT GACGAGCATC ACAAAAATCG ACGCTCAAGT CAGAGGTGGC
     TTCCGGTCCT TGGCATTTTT CCGGCGCAAC GACCGCAAAA AGGTATCCGA GGCGGGGGGA CTGCTCGTAG TGTTTTTAGC TGCGAGTTCA GTCTCCACCG
```

FIG. 41P

```
                                          scrFI
                 scrFI     mvaI
                 mvaI                     ecoRII
                 ecoRII    dsaV                                                    bslI
                 dsaV      bstNI                            hinPI                          aciI      mspI
                 bstNI                    apyI[dcm+]        bssSI                               fnu4HI     hpaII
                 apyI[dcm+]           bsaJI      aluI  mnlI       hhaI/cfoI                      bsoFI    bsaWI         aciI
4801 GAAACCCGAC AGGACTATAA AGATACCAGG CGTTTCCCCC TGGAAGCTCC CTCGTGCGCT CTCCTGTTCC GACCCTGCCG CTTACCGGAT ACCTGTCCGC
     CTTTGGGCTG TCCTGATATT TCTATGGTCC GCAAAGGGGG ACCTTCGAGG GAGCACGCGA GAGGACAAGG CTGGGACGGC GAATGGCCTA TGGACAGGCG

                                                                                                            hgiAI/aspHI
                                                                                                            bsp1286
                                                                                                            bsiHKAI
                                                                                                            bmyI
                                                                                                            apaLI/snoI
                      hinPI                                                                                 alw44I/snoI
                      hhaI/cfoI                                                                  aluI
                      haeII          aluI      scfI       ddeI
4901 CTTTCTCCCT TCGGGAAGCG TGGCGCTTTC TCATAGCTCA CGCTGTAGGT ATCTCAGTTC GGTGTAGGTC GTTCGCTCCA AGCTGGGCTG TGTGCACGAA
     GAAAGAGGGA AGCCCTTCGC ACCGCGAAAG AGTATCGAGT GCGACATCCA TAGAGTCAAG CCACATCCAG CAAGCGAGGT TCGACCCGAC ACACGTGCTT

                                                                                                        alwNI[dcm-]
                                                                                                       fnu4HI
                                                                  mspI                                 bsoFI
                  fnu4HI                                          hpaII                             fnu4HI
                  bsoFI                                           scrFI                             bsoFI
                nspBII                   maeIII                   nciI                              bbvI
                aciI  hinPI            mspI                       dsaV                                         maeIII
             mcrI bbvI                 bsaWI          pleI        cauII                        bsrI      bbvI      bsrI
             bsiEI      hhaI/cfoI      hpaII          hinfI
5001 CCCCCCGTTC AGCCCGACCG CTGCGCCTTA TCCGGTAACT ATCGTCTTGA GTCCAACCCG GTAAGACACG ACTTATCGCC ACTGGCAGCA GCCACTGGTA
     GGGGGGCAAG TCGGGCTGGC GACGCGGAAT AGGCCATTGA TAGCAGAACT CAGGTTGGGC CATTCTGTGC TGAATAGCGG TGACCGTCGT CGGTGACCAT

                                                                 bslI              rmaI
                                                                 haeIII/palI       maeI                     hinPI
                 mnlI          aciI    scfI                      haeI              bfaI                     hhaI/cfoI
5101 ACAGGATTAG CAGAGCGAGG TATGTAGGCG GTGCTACAGA GTTCTTGAAG TGGTGGCCTA ACTACGGCTA CACTAGAAGG ACAGTATTTG GTATCTGCGC
     TGTCCTAATC GTCTCGCTCC ATACATCCGC CACGATGTCT CAAGAACTTC ACCACCGGAT TGATGCCGAT GTGATCTTCC TGTCATAAAC CATAGACGCG
```

FIG. 41Q

```
                                                    mspI
                                                    hpaII
                                                  sau3AI
                                                  mboI/ndeII[dam-]
                                                  dpnI[dam+]                                                fnu4HI
                                                  dpnII[dam-]       nspBII                                  bsoFI
              maeIII                                                                                        bbvI
        eco57I bsrI                          aluI  alwI[dam-]        aciI      aciI                 cac8I
5201 TCTGCTGAAG CCAGTTACCT TCGGAAAAAG AGTTGGTAGC TCTTGATCCG GCAAACAAAC CACCGCTGGT AGCGGTGGTT TTTTTGTTTG CAAGCAGCAG
     AGACGACTTC GGTCAATGGA AGCCTTTTTC TCAACCATCG AGAACTAGGC CGTTTGTTTG GTGGCGACCA TCGCCACCAA AAAAACAAAC GTTCGTCGTC

                                             sau3AI
                                       sau3AI  mboI/ndeII[dam-]
                                       mboI/ndeII[dam-]
        hinPI           sau3AI   mboII[dam-] dpnI[dam+]
        hhaI/cfoI       mboI/ndeII[dam-]     dpnII[dam-]
       thaI             dpnI[dam+]   dpnI[dam+]                                                tru9I        nlaIII
       fnuDII/mvnI      dpnII[dam-]  dpnII[dam-]                                               mseI         rcaI
       bstUI           bstYI/xhoII   alwI[dam-]                                               maeII        bspHI
       bsh1236I        alwI[dam-]  bstYI/xhoII                   hgaI ddeI
5301 ATTACGCGCA GAAAAAAAGG ATCTCAAGAA GATCCTTTGA TCTTTTCTAC GGGGTCTGAC GCTCAGTGGA ACGAAAACTC ACGTTAAGGG ATTTTGGTCA
     TAATGCGCGT CTTTTTTTCC TAGAGTTCTT CTAGGAAACT AGAAAAGATG CCCCAGACTG CGAGTCACCT TGCTTTTGAG TGCAATTCCC TAAAACCAGT

                                     sau3AI
                                     mboI/ndeII[dam-]
                                   rmaI
                                hphI  dpnI[dam+]
                             mboII[dam-]
                           sau3AI    maeI       tru9I
                           mboI/ndeII[dam-]     mseI
                           dpnI[dam+]   dpnII[dam-]
                           dpnII[dam-]  alwI[dam-]   tru9I           tru9I
                          bstYI/xhoII  bstYI/xhoII   mseI            mseI
                          alwI[dam-] bfaI     ahaIII/draI          ahaIII/draI                               maeIII
5401 TGAGATTATC AAAAAGGATC TTCACCTAGA TCCTTTTAAA TTAAAAATGA AGTTTTAAAT CAATCTAAAG TATATATGAG TAAACTTGGT CTGACAGTTA
     ACTCTAATAG TTTTTCCTAG AAGTGGATCT AGGAAAATTT AATTTTTACT TCAAAATTTA GTTAGATTTC ATATATACTC ATTTGAACCA GACTGTCAAT

                       nlaIV            sau3AI
                       hgiCI            mboI/ndeII[dam-]                 pleI
             tru9I     banI             dpnI[dam+]                       hinfI
             mseI     mnlI       ddeI   dpnII[dam-]        fokI          ahdI/eam1105I                        mnlI
5501 CCAATGCTTA ATCAGTGAGG CACCTATCTC AGCGATCTGT CTATTTCGTT CATCCATAGT TGCCTGACTC CCCGTCGTGT AGATAACTAC GATACGGGAG
     GGTTACGAAT TAGTCACTCC GTGGATAGAG TCGCTAGACA GATAAAGCAA GTAGGTATCA ACGGACTGAG GGGCAGCACA TCTATTGATG CTATGCCCTC
```

FIG. 41R

TOTESO"95292260

```
                                             bsmAI
                                             bsaI
                                          thaI                   bpmI/gsuI[dcm-]
                      bsrI                fnuDII/mvnI        mspI                                  mspI
                  sau96I    fnu4HI        bstUI              hpaII                                 hpaII    haeIII/palI
                  nlaIV     bsoFI         bsh1236I          cfr10I/bsrFI                          bglI     sau96I hinPI
                  haeIII/palI  bsrDI     aciI            hphI  nlaIV                           cac8I      asuI   hhaI/cfoI
                  asuI      bbvI
5601 GGCTTACCAT CTGGCCCCAG TGCTGCAATG ATACCGCGAG ACCCACGCTC ACCGGCTCCA GATTTATCAG CAATAAACCA GCCAGCCGGA AGGGCCGAGC
     CCGAATGGTA GACCGGGGTC ACGACGTTAC TATGGCGCTC TGGGTGCGAG TGGCCGAGGT CTAAATAGTC GTTATTTGGT CGGTCGGCCT TCCCGGCTCG

                                                             scrFI
                                                             nciI
                                                             mspI                                             maeII
                                                             hpaII   rmaI                                   hinPI
                                                             dsaV    maeI                                   hhaI/cfoI
                                                  tru9I      cauII   bfaI                    tru9I         mstI psp1406I
             sau96I              mnlI    bsrI     mseI             aluI                  bsrI mseI         aviII/fspI
             avaII             aciI    fokI      aseI/asnI/vspI
             asuI
5701 GCAGAAGTGG TCCTGCAACT TTATCCGCCT CCATCCAGTC TATTAATTGT TGCCGGGAAG CTAGAGTAAG TAGTTCGCCA GTTAATAGTT TGCGCAACGT
     CGTCTTCACC AGGACGTTGA AATAGGCGGA GGTAGGTCAG ATAATTAACA ACGGCCCTTC GATCTCATTC ATCAAGCGGT CAATTATCAA ACGCGTTGCA

                                                                                                 sau3AI
                                                                                                 mboI/ndeII[dam-]
                 cac8I                                                               sau3AI      dpnI[dam+]
               scfI                                                         nlaIV    mboI/ndeII[dam-]  dpnII[dam-]
               pstI                                                        mspI      dpnI[dam+]     nlaIII      nlaIII
              fnu4HI                                                      bsaWI      dpnII[dam-] maeIII  alwI[dam-]
              bsoFI     msII                                           aluI hpaII
              bbvI   sfaNI          maeIII
          bsrDI bsgI
5801 TGTTGCCATT GCTGCAGGCA TCGTGGTGTC ACGCTCGTCG TTTGGTATGG CTTCATTCAG CTCCGGTTCC CAACGATCAA GGCGAGTTAC ATGATCCCCC
     ACAACGGTAA CGACGTCCGT AGCACCACAG TGCGAGCAGC AAACCATACC GAAGTAAGTC GAGGCCAAGG GTTGCTAGTT CCGCTCAATG TACTAGGGGG

                                             sau3AI
                                             mboI/ndeII[dam-]                 aciI
                                             dpnI[dam+]                      fnu4HI
                                        mnlI dpnII[dam-]                     bsoFI
                                     sau96I pvuI/bspCI                     haeIII/palI                fnu4HI
                                     avaII   mcrI                          eaeI               nlaIII   bsoFI
                                     asuI    bsiEI                         cfrI               msII     bbvI
                      aciI    aluI
5901 ATGTTGTGCA AAAAAGCGGT TAGCTCCTTC GGTCCTCCGA TCGTTGTCAG AAGTAAGTTG GCCGCAGTGT TATCACTCAT GGTTATGGCA GCACTGCATA
     TACAACACGT TTTTTCGCCA ATCGAGGAAG CCAGGAGGCT AGCAACAGTC TTCATTCAAC CGGCGTCACA ATAGTGAGTA CCAATACCGT CGTGACGTAT
```

FIG. 41S

```
                                                                                   mcrI
                                                                                   bsiEI
                                                                                   bcgI
                                                                                fnu4HI
                                                 rsaI                           bsoFI
                                           bsrI  scaI                           aciI
                fokI                                               ddeI
            nlaIII        sfaNI       maeIII hphI csp6I
6001 ATTCTCTTAC TGTCATGCCA TCCGTAAGAT GCTTTTCTGT GACTGGTGAG TACTCAACCA AGTCATTCTG AGAATAGTGT ATGCGGCGAC CGAGTTGCTC
     TAAGAGAATG ACAGTACGGT AGGCATTCTA CGAAAAGACA CTGACCACTC ATGAGTTGGT TCAGTAAGAC TCTTATCACA TACGCCGCTG GCTCAACGAG

        hgaI
       hinlI/acyI                                                                                      sau3AI
        ahaII/bsaHI         hinPI                                                                      mboI/ndeII[dam-]
      mspI                  hhaI/cfoI                hgiAI/aspHI                                       dpnI[dam+]
      hpaII                thaI                      bsp1286            maeII                          dpnII[dam-]
     scrFI                 fnuDII/mvnI          tru9I bsiHKAI          psp1406I                       bstYI/xhoII
     nciI                  bstUI                mseI  bmyI           xmnI                             alwI[dam-]
     dsaV                  bsh1236I           ahaIII/draI            asp700   mboII
     cauII hincII/hindII  aciI
6101 TTGCCCGGCG TCAACACGGG ATAATACCGC GCCACATAGC AGAACTTTAA AAGTGCTCAT CATTGGAAAA CGTTCTTCGG GGCGAAAACT CTCAAGGATC
     AACGGGCCGC AGTTGTGCCC TATTATGGCG CGGTGTATCG TCTTGAAATT TTCACGAGTA GTAACCTTTT GCAAGAAGCC CCGCTTTTGA GAGTTCCTAG

                 bsrI                  hgiAI/aspHI
               sau3AI    taqI          bsp1286         eco57I
               mboI/ndeII[dam-]        bsiHKAI        mboII[dam-]
               dpnI[dam+]              bmyI         sau3AI    sfaNI
               dpnII[dam-]             apaLI/snoI   mboI/ndeII[dam-]
               alwI[dam-]              alw44I/snoI  dpnI[dam+]
      nspBII                                        dpnII[dam-]        hphI         hphI
      aciI    bstYI/xhoII   maeIII    bssSI
6201 TTACCGCTGT TGAGATCCAG TTCGATGTAA CCCACTCGTG CACCCAACTG ATCTTCAGCA TCTTTTACTT TCACCAGCGT TTCTGGGTGA GCAAAAACAG
     AATGGCGACA ACTCTAGGTC AAGCTACATT GGGTGAGCAC GTGGGTTGAC TAGAAGTCGT AGAAAATGAA AGTGGTCGCA AAGACCCACT CGTTTTTGTC

                 aciI                                          mboII
                fnu4HI                                      earI/ksp632I  sspI
                bsoFI              mslI
6301 GAAGGCAAAA TGCCGCAAAA AAGGGAATAA GGGCGACACG GAAATGTTGA ATACTCATAC TCTTCCTTTT TCAATATTAT TGAAGCATTT ATCAGGGTTA
     CTTCCGTTTT ACGGCGTTTT TTCCCTTATT CCCGCTGTGC CTTTACAACT TATGAGTATG AGAAGGAAAA AGTTATAATA ACTTCGTAAA TAGTCCCAAT
```

FIG. 41T

```
                                                                                     hinPI
                                                                                    thaI
                                                                                    fnuDII/mvnI
                                                                                    bstUI                              maeII
     nlaIII                                                                         bsh1236I                           hinlI/acyI
     rcaI                                                                          aciI                                ahaII/bsaHI
     bspHI  aciI                                                               nlaIV  hhaI/cfoI                        aatII ddeI
   bsmAI  bsrBI
6401 TTGTCTCATG AGCGGATACA TATTTGAATG TATTTAGAAA AATAAACAAA TAGGGGTTCC GCGCACATTT CCCCGAAAAG TGCCACCTGA CGTCTAAGAA
     AACAGAGTAC TCGCCTATGT ATAAACTTAC ATAAATCTTT TTATTTGTTT ATCCCCAAGG CGCGTGTAAA GGGGCTTTTC ACGGTGGACT GCAGATTCTT

                                                       sau96I
                                                       haeIII/palI
                                                       asuI        mboII
                                                      eco0109I/draII
             nlaIII                                  mnlI        bpuAI
             rcaI    tru9I                         bssSI         bbsI
             bspHI   mseI
6501 ACCATTATTA TCATGACATT AACCTATAAA AATAGGCGTA TCACGAGGCC CTTTCGTCTT CAA   (SEQ ID NO.61)
     TGGTAATAAT AGTACTGTAA TTGGATATTT TTATCCGCAT AGTGCTCCGG GAAAGCAGAA GTT
```

FIG. 41U

```
>length: 6563

aatII(GACGTC):         1645 6489
acc65I(GGTACC):        403 823
accI(GTMKAC):          1093 1963 4449
accIII(TCCGGA):        3867[dam-]
aciI(CCGC):            178 542 805 877 1340 1750 1826 2011 2039 2043 2182 2242 2384 2492 2501 2504
                       2628 2781 2784 2787 2906 2926 3005 3045 3094 3141 3226 3241 3309 3342 3367 3412
                       3436 3448 3490 3544 3597 3613 3619 3700 3838 3967 3970 3981 4139 4155 4210 4266
                       4351 4390 4400 4442 4467 4505 4518 4544 4561 4604 4611 4632 4723 4751 4878 4897
                       5018 5128 5263 5272 5634 5725 5916 5962 6083 6127 6204 6313 6412 6459
acyI                   see hinlI
aflIII(ACRYGT):        1307 4678
ageI(ACCGGT):          1788
ahaII/bsaHI(GRCGYC):   1645 1813 2616 2637 2751 3408 6107 6489
ahaIII/draI(TTTAAA):   5435 5454 6146
ahdI/eam1105I(GACNNNNNGTC): 346 5566
aluI(AGCT):            72 121 252 320 398 532 589 648 1126 1144 1167 1325 1386 1906 2054 2075 2126
                       2218 2233 2889 3292 4202 4259 4270 4319 4338 4619 4845 4935 4981 5238 5759 5859
                       5922
alw44I/snoI(GTGCAC):   1831 4494 4992 6238
alwI[dam-](GGATC):     412 413 712 713 1171 1471 2578 2579 3300 3870 5245 5319 5331 5416 5429 5893
                       6196 6214
alwNI[dcm-](CAGNNNCTG): 1117 1385 5089
apaI(GGGCCC):          1695
apaLI/snoI(GTGCAC):    1831 4494 4992 6238
apoI(RAATTY):          1 391 4093
apyI[dcm+](CCWGG):     640 999 1347 1357 1449 1665 1713 1755 1764 2333 3262 3645 4705 4826 4839
aseI/asnI/vspI(ATTAAT): 5742
asnI                   see aseI
asp700(GAANNNNTTC):    905 930 4234 6166
asp718(GGTACC):        403 823
aspHI                  see hgiAI
aspI                   see tth111I
asuI(GGNCC):           1119 1195 1425 1434 1446 1512 1695 1696 1752 2155 2375 2727 3002 3090 3339 3463
```

FIG. 41V

Stop Template Primer

SL.97.2 5' CAT GGT ATA GGT <u>TAA</u> ACT TAT TTA CAC 3' (SEQ ID NO.63)

NNS Randomization Primer

SL.97.3 5' CAT GGT ATA GGT <u>NNS</u> ACT TAT TTA CAC 3' (SEQ ID NO.64)

FIG. 42

Randomization of Position N35 of Variable Light Chain CDR-1
Amino Acid Frequency

Phage Display (NNS Codon Library) Sort #3

Amino Acid	Frequency	% Total	IC50 (nM)
Asparagine (wt)	1	5.6	4.9
Glycine	6	16.6	3.1
Aspartic Acid	3	16.6	3.1
Glutamic Acid	4	22.2	0.1
Alanine	2	5.6	0.2
Lysine	1	5.6	ND
Serine	1	1.9	ND

FIG. 43A

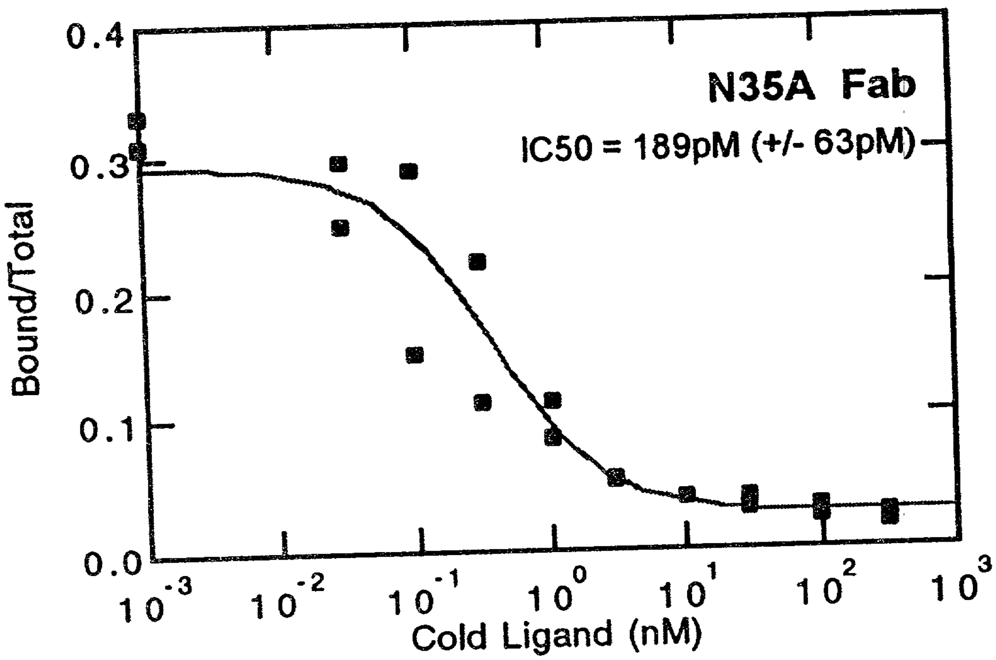


FIG. 43B

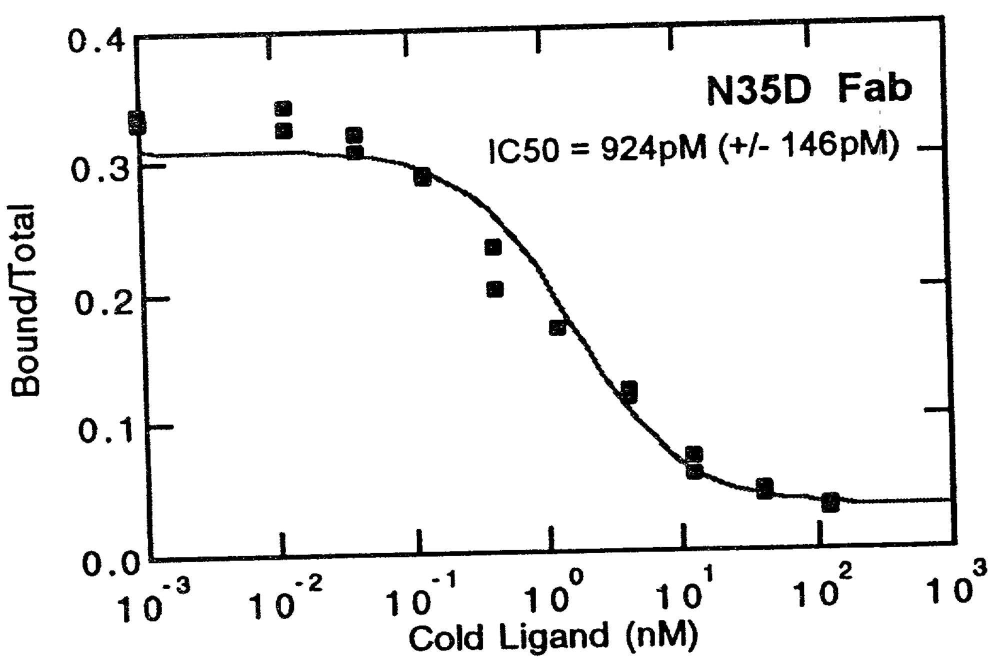


FIG. 43C

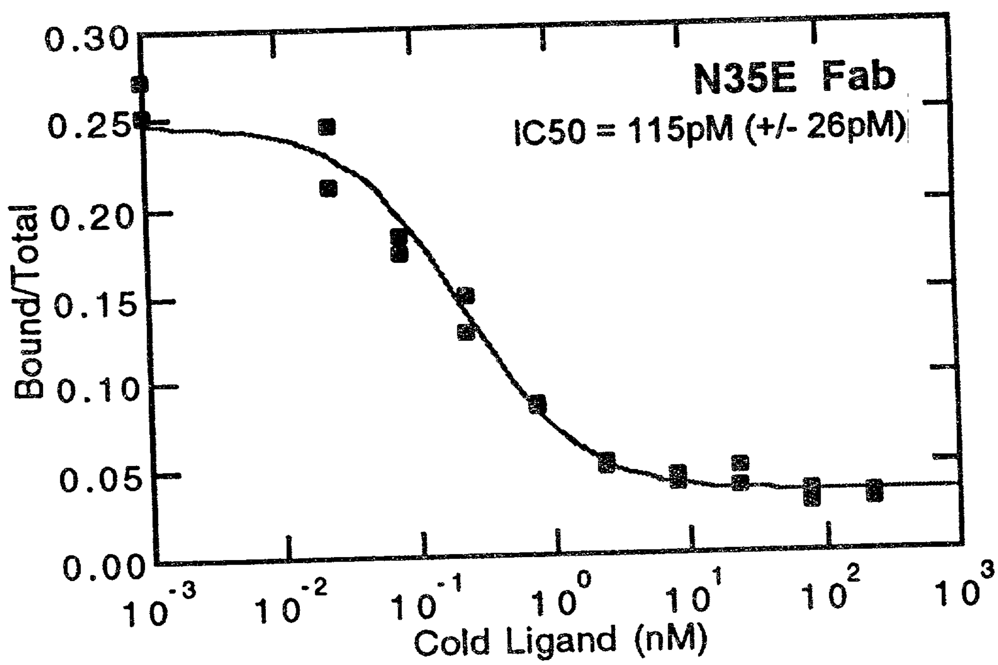


FIG. 43D

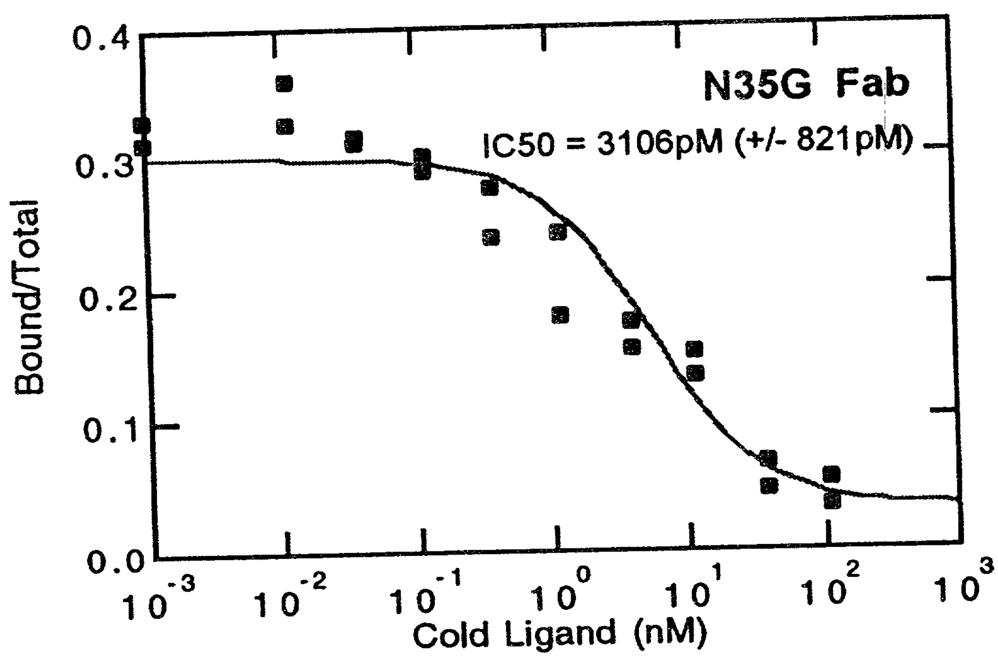
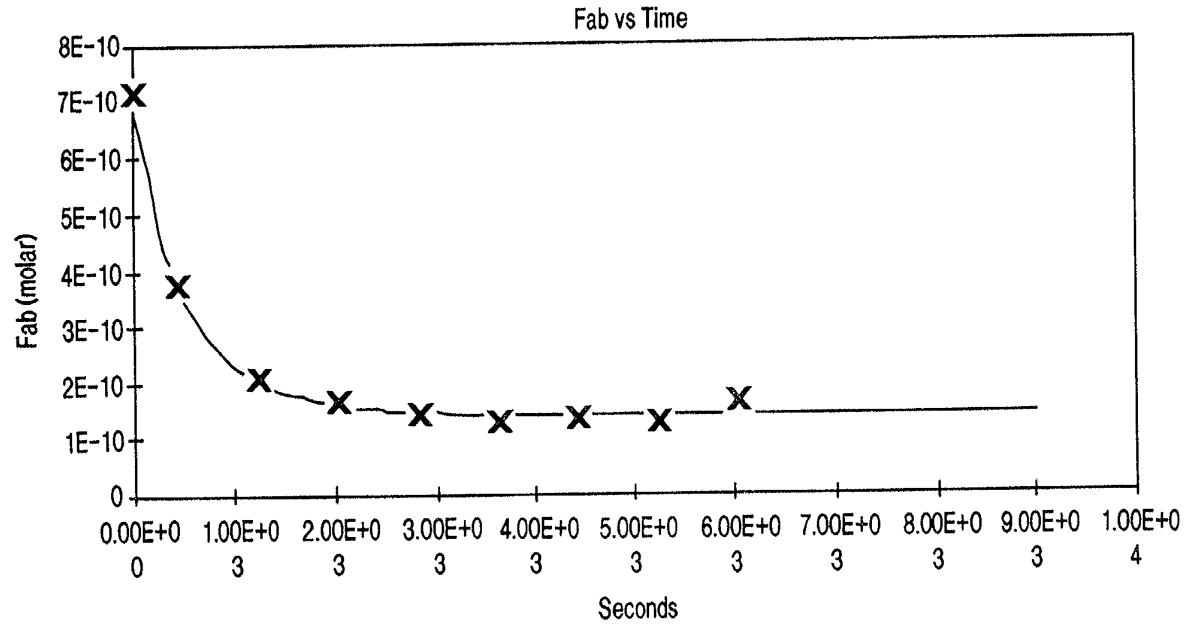


FIG. 43E



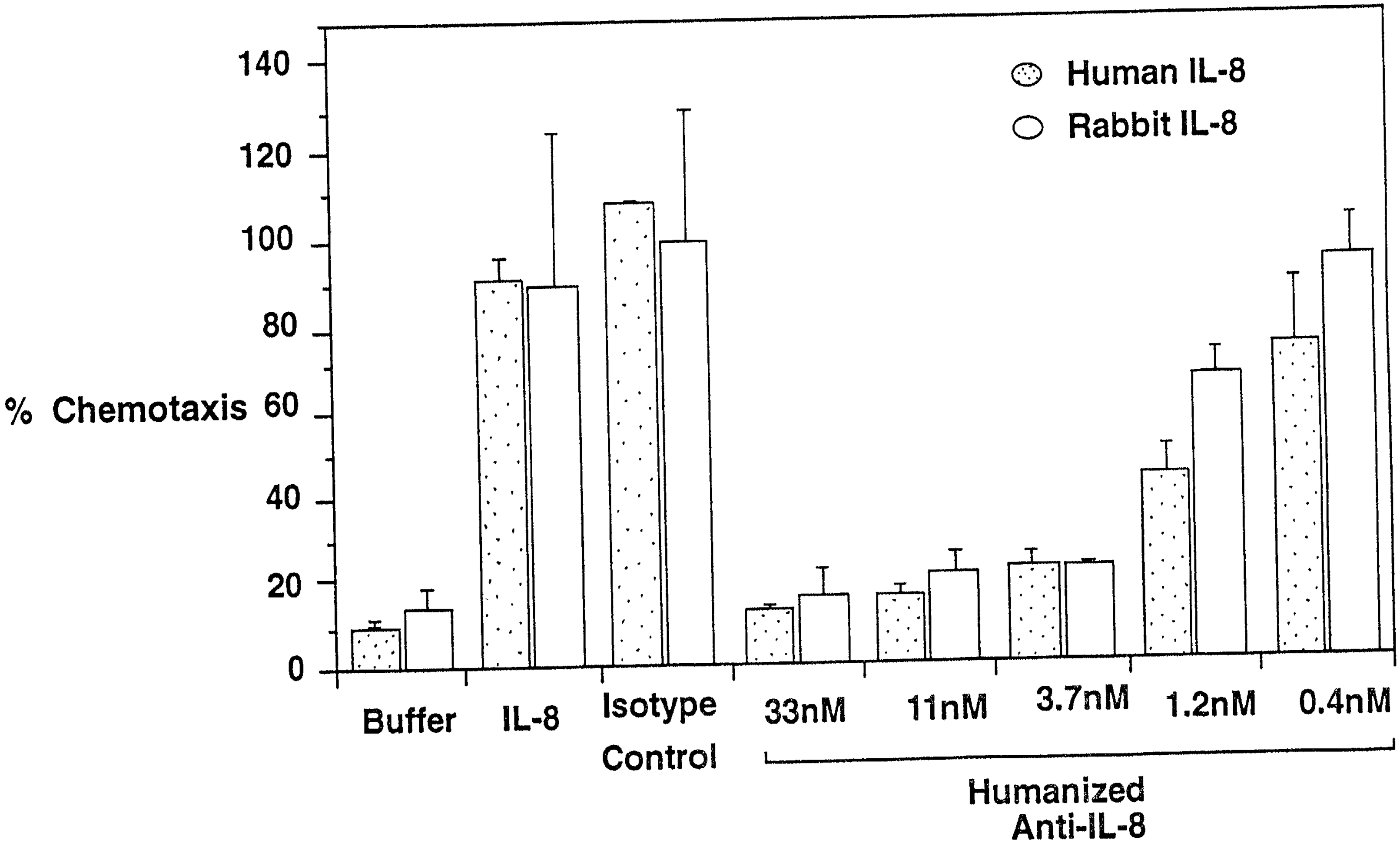
Representative Conc versus Time Plot. Shown is the kinetic data for 6G4V11N35A.F(ab')2

SAMPLE	ka	kd	Kd
6G4V11N35A-Fab	ND	ND	114pM
6G4V11N35A-F(ab')$_2$	2.0×10^6	2.1×10^{-4}	109pM
6G4V11N35E-Fab	4.7×10^6	2.6×10^{-4}	54pM

FIG. 44

```
  1 ATGAAAAAGA ATATCGCATT TCTTCTTGCA TCTATGTTCG TTTTTTCTAT TGCTACAAAC
    TACTTTTTCT TATAGCGTAA AGAAGAACGT AGATACAAGC AAAAAAGATA ACGATGTTTG
-23 M  K  K  N   I  A  F   L  L  A   S  M  F  V   F  S  I   A  T  N

 61 GCATACGCTG ATATCCAGAT GACCCAGTCC CCGAGCTCCC TGTCCGCCTC TGTGGGCGAT
    CGTATGCGAC TATAGGTCTA CTGGGTCAGG GGCTCGAGGG ACAGGCGGAG ACACCCGCTA
 -3 A  Y  A  D   I  Q  M   T  Q  S   P  S  S  L   S  A  S   V  G  D

121 AGGGTCACCA TCACCTGCAG GTCAAGTCAA AGCTTAGTAC ATGGTATAGG TGAGACGTAT
    TCCCAGTGGT AGTGGACGTC CAGTTCAGTT TCGAATCATG TACCATATCC ACTCTGCATA
 18 R  V  T  I   T  C  R   S  S  Q   S  L  V  H   G  I  G   E  T  Y

181 TTACACTGGT ATCAACAGAA ACCAGGAAAA GCTCCGAAAC TACTGATTTA CAAAGTATCC
    AATGTGACCA TAGTTGTCTT TGGTCCTTTT CGAGGCTTTG ATGACTAAAT GTTTCATAGG
 38 L  H  W  Y   Q  Q  K   P  G  K   A  P  K  L   L  I  Y   K  V  S

241 AATCGATTCT CTGGAGTCCC TTCTCGCTTC TCTGGATCCG GTTCTGGGAC GGATTTCACT
    TTAGCTAAGA GACCTCAGGG AAGAGCGAAG AGACCTAGGC CAAGACCCTG CCTAAAGTGA
 58 N  R  F  S   G  V  P   S  R  F   S  G  S  G   S  G  T   D  F  T

301 CTGACCATCA GCAGTCTGCA GCCAGAAGAC TTCGCAACTT ATTACTGTTC ACAGAGTACT
    GACTGGTAGT CGTCAGACGT CGGTCTTCTG AAGCGTTGAA TAATGACAAG TGTCTCATGA
 78 L  T  I  S   S  L  Q   P  E  D   F  A  T  Y   Y  C  S   Q  S  T

361 CATGTCCCGC TCACGTTTGG ACAGGGTACC AAGGTGGAGA TCAAACGAAC TGTGGCTGCA
    GTACAGGGCG AGTGCAAACC TGTCCCATGG TTCCACCTCT AGTTTGCTTG ACACCGACGT
 98 H  V  P  L   T  F  G   Q  G  T   K  V  E  I   K  R  T   V  A  A

421 CCATCTGTCT TCATCTTCCC GCCATCTGAT GAGCAGTTGA AATCTGGAAC TGCTTCTGTT
    GGTAGACAGA AGTAGAAGGG CGGTAGACTA CTCGTCAACT TTAGACCTTG ACGAAGACAA
118 P  S  V  F   I  F  P   P  S  D   E  Q  L  K   S  G  T   A  S  V

481 GTGTGCCTGC TGAATAACTT CTATCCCAGA GAGGCCAAAG TACAGTGGAA GGTGGATAAC
    CACACGGACG ACTTATTGAA GATAGGGTCT CTCCGGTTTC ATGTCACCTT CCACCTATTG
138 V  C  L  L   N  N  F   Y  P  R   E  A  K  V   Q  W  K   V  D  N

541 GCCCTCCAAT CGGGTAACTC CCAGGAGAGT GTCACAGAGC AGGACAGCAA GGACAGCACC
    CGGGAGGTTA GCCCATTGAG GGTCCTCTCA CAGTGTCTCG TCCTGTCGTT CCTGTCGTGG
158 A  L  Q  S   G  N  S   Q  E  S   V  T  E  Q   D  S  K   D  S  T

601 TACAGCCTCA GCAGCACCCT GACGCTGAGC AAAGCAGACT ACGAGAAACA CAAAGTCTAC
    ATGTCGGAGT CGTCGTGGGA CTGCGACTCG TTTCGTCTGA TGCTCTTTGT GTTTCAGATG
178 Y  S  L  S   S  T  L   T  L  S   K  A  D  Y   E  K  H   K  V  Y

661 GCCTGCGAAG TCACCCATCA GGGCCTGAGC TCGCCCGTCA CAAAGAGCTT CAACAGGGGA
    CGGACGCTTC AGTGGGTAGT CCCGGACTCG AGCGGGCAGT GTTTCTCGAA GTTGTCCCCT
198 A  C  E  V   T  H  Q   G  L  S   S  P  V  T   K  S  F   N  R  G
                                                      (SEQ ID NO.65)
721 GAGTGTTAAG CTGATCCTCT ACGCCGGACG CATCGTGGCC CTAGTACGCA ACTAGTCGTA
    CTCACAATTC GACTAGGAGA TGCGGCCTGC GTAGCACCGG GATCATGCGT TGATCAGCAT
218 E  C  O (SEQ ID NO.62)
```

FIG. 45



Human IL-8
Rabbit IL-8
% Chemotaxis
140
120
100
80
60
40
20
0
Buffer
IL-8
Isotype Control
33nM
11nM
3.7nM
1.2nM
0.4nM
Humanized Anti-IL-8

FIG. 46

N35AH1upr

5'-CT**A**GTGCAGTCTGGCGGTGGCCTGGTGCAGCCAGGGGGCTCACTCCGTTTGTCCTGTGCAGCTTCTGGCTACTCCTTC-3'
(SEQ ID NO.66)

N35AH1lwr

5'-TCGAGAAGGAGTAGCCAGAAGCTGCACAGGACAAACGGAGTGAGCCCCCTGGCTGCACCAGGCCACCGCCAGACTGCACT
(SEQ ID NO.67)

AG-3'

Bold indicates nucleotide change destroying PvuII site.

FIG. 47

```
> length: 8120 (circular)
>This has the pSVI backbone with the pRK7 cloning linker (pSVI7) and the intron DHFR(ID)
>made from pSVI.WTSD.D by adding a linearization linker(LL) into the Hpal site

       cac8I
      aluI
      sstI                                                                           scrFI
      sacI                                    sau3AI  aluI                            mvaI
      hgiJII                                  mboI/ndeII[dam-]                        ecoRII
      hgiAI/aspHI                             dpnI[dam+]                              dsaV
      ecl136II                               pvuI/bspCI                               bstNI
      bsp1286                              pleI dpnII[dam-]                           apyI[dcm+]
      bsiHKAI                              hinfI  taqI[dam-]                         bsaJI
      bmyI                              rmaI   mcrI    pvuII                     bsmFI   nlaIV     cac8I
      banII                             maeI   bsiEI   nspBII
     taqI                               bfaI  taqI[dam-]
  1 TTCGAGCTCG CCCGACATTG ATTATTGACT AGAGTCGATC GACAGCTGTG GAATGTGTGT CAGTTAGGGT GTGGAAAGTC CCCAGGCTCC CCAGCAGGCA
    AAGCTCGAGC GGGCTGTAAC TAATAACTGA TCTCAGCTAG CTGTCGACAC CTTACACACA GTCAATCCCA CACCTTTCAG GGGTCCGAGG GGTCGTCCGT

                                                            scrFI                           sfaNI
            sfaNI                         scrFI       mvaI                                  ppu10I
           ppu10I                         mvaI             ecoRII                           nsiI/avaIII
           nsiI/avaIII                    ecoRII                                       nlaIII
          nlaIII                          dsaV        dsaV                               sphI
         sphI                             bstNI       bstNI                                 nspI
         nspI                             apyI[dcm+]        apyI[dcm+]                      nspHI
         nspHI                           sexAI           bsaJI                              cac8I
         cac8I                                        bsmFI   nlaIV      cac8I
101 GAAGTATGCA AAGCATGCAT CTCAATTAGT CAGCAACCAG GTGTGGAAAG TCCCCAGGCT CCCCAGCAGG CAGAAGTATG CAAAGCATGC ATCTCAATTA
    CTTCATACGT TTCGTACGTA GAGTTAATCA GTCGTTGGTC CACACCTTTC AGGGGTCCGA GGGGTCGTCC GTCTTCATAC GTTTCGTACG TAGAGTTAAT

                                                                              nlaIII
                                                                              styI
                                                                              ncoI
                                                                         bslI dsaI
           aciI                          aciI                            aciI bsaJI
          bsmFI             aciI  fokI              aciI bsrI  aciI
201 GTCAGCAACC ATAGTCCCGC CCCTAACTCC GCCCATCCCG CCCCTAACTC CGCCCAGTTC CGCCCATTCT CCGCCCCATG GCTGACTAAT TTTTTTTATT
    CAGTCGTTGG TATCAGGGCG GGGATTGAGG CGGGTAGGGC GGGGATTGAG GCGGGTCAAG GCGGGTAAGA GGCGGGGTAC CGACTGATTA AAAAAAATAA
```

FIG. 48A

```
                                                                                         rmaI
                                                                                         maeI                                haeIII/palI
       fnu4HI                                                                           styI                  aluI          mcrI
       bsoFI                                                                            bsaJI               rmaI            eagI/xmaIII/eclXI
       bglI                                                                             blnI                maeI            eaeI
       sfiI                                                                             avrII[dam-]         bfaI            cfrI
       haeIII/palI                                                                    haeIII/palI           nheI            bsiEI
     mnlI    mnlI      ddeI                                         mnlI              stuI                  cac8I          mspI
  haeIII/palI bsaJI  mnlI    aluI                              mnlI                   haeI                aluI             hpaII
mnlI bsaJI aciI   haeIII/palI                                  bseRI                  mnlI bfaI
301 TATGCAGAGG CCGAGGCCGC CTCGGCCTCT GAGCTATTCC AGAAGTAGTG AGGAGGCTTT TTTGGAGGCC TAGGCTTTTG CAAAAGCTA GCTTATCCGG
    ATACGTCTCC GGCTCCGGCG GAGCCGGAGA CTCGATAAGG TCTTCATCAC TCCTCCGAAA AAACCTCCGG ATCCGAAAAC GTTTTCGAT CGAATAGGCC

                          tfiI
                          hinfI                                                                         fnu4HI
    scrFI              aciI                                                                             bsoFI
    nciI               thaI                                                                             bbvI
    mspI               fnuDII/mvnI                          aciI                                       nspBII
    hpaII              bstUI                   maeII   rsaI                                             aciI        nlaIII
    dsaV               bsh1236I             maeIII   csp6I   scfI                  mnlI
    cauII
401 CCGGGAACGG TGCATTGGAA CGCGGATTCC CCGTGCCAAG AGTGACGTAA GTACCGCCTA TAGAGCGATA AGAGGATTTT ATCCCCGCTG CCATCATGGT
    GGCCCTTGCC ACGTAACCTT GCGCCTAAGG GGCACGGTTC TCACTGCATT CATGGCGGAT ATCTCGCTAT TCTCCTAAAA TAGGGGCGAC GGTAGTACCA
                                                 ^splice donor                                             DHFR ATG^

                                                                               haeIII/palI
                                                                               haeI
                                                                               scrFI
                                                                               mvaI      bsrBI
                                                                               ecoRII
                                                                               dsaV
                                                                               bstNI      aciI                   rsaI
                                  pflMI                                        apyI[dcm+]          xmnI          csp6I
                                  bslI                         bsmAI                                asp700        scaI
                               bsmFI                           bsaI          bsaJI   mnlI   ddeI
    taqI         sfaNI
501 TCGACCATTG AACTGCATCG TCGCCGTGTC CCAAAATATG GGGATTGGCA AGAACGGAGA CCTACCCTGG CCTCCGCTCA GGAACGAGTT CAAGTACTTC
    AGCTGGTAAC TTGACGTAGC AGCGGCACAG GGTTTTATAC CCCTAACCGT TCTTGCCTCT GGATGGGACC GGAGGCGAGT CCTTGCTCAA GTTCATGAAG
```

FIG. 48B

```
                                                                         scrFI
                                                                         mvaI
                                                                         ecoRII
                                                                         dsaV
          eco57I                                                         bstNI                    tfiI      tru9I
         mboII                   tfiI                                    apyI[dcm+]               hinfI     mseI
        earI/ksp632I             hinfI   hphI                           sexAI           ddeI mboII taqI    ahaIII/draI
       mnlI                     alwNI[dcm-]
601 CAAAGAATGA CCACAACCTC TTCAGTGGAA GGTAAACAGA ATCTGGTGAT TATGGGTAGG AAAACCTGGT TCTCCATTCC TGAGAAGAAT CGACCTTTAA
    GTTTCTTACT GGTGTTGGAG AAGTCACCTT CCATTTGTCT TAGACCACTA ATACCCATCC TTTTGGACCA AGAGGTAAGG ACTCTTCTTA GCTGGAAATT

                                                              sstI
                                                              sacI
                                                              hgiJII
                                                              hgiAI/aspHI
                                                              ecl136II
                                                              bsp1286
                                                              bsiHKAI
                                                              bmyI
                                                           mnlI aluI                                 tru9I
      tru9I                                             bssSI  banII                                aflII/bfrI
      mseI           ddeI                            bslI   bseRI          bstXI       fokI sfaNI mseI
     aseI/asnI/vspI
701 AGGACAGAAT TAATATAGTT CTCAGTAGAG AACTCAAAGA ACCACCACGA GGAGCTCATT TTCTTGCCAA AAGTTTGGAT GATGCCTTAA GACTTATTGA
    TCCTGTCTTA ATTATATCAA GAGTCATCTC TTGAGTTTCT TGGTGGTGCT CCTCGAGTAA AAGAACGGTT TTCAAACCTA CTACGGAATT CTGAATAACT

                                                                                      haeIII/palI
                                                                                     haeI
                                                                    scrFI       scrFI
                                                                    mvaI             mvaI
                                                                    ecoRII      ecoRII
                                                                    dsaV   tfiI dsaV
     mspI                                                           bstNI   nlaIII    bstNI     ddeI pleI
     hpaII                                                          apyI[dcm+]  hinfI apyI[dcm+]     hinfI
    bsaWI                  accI nlaIII              mnlI
801 ACAACCGGAA TTGGCAAGTA AAGTAGACAT GGTTTGGATA GTCGGAGGCA GTTCTGTTTA CCAGGAAGCC ATGAATCAAC CAGGCCACCT TAGACTCTTT
    TGTTGGCCTT AACCGTTCAT TTCATCTGTA CCAAACCTAT CAGCCTCCGT CAAGACAAAT GGTCCTTCGG TACTTAGTTG GTCCGGTGGA ATCTGAGAAA
```

FIG. 48C

```
                                                                                                              hgaI
                                                                                                             hinlI/acyI
                                                                                                             ahaII/bsaHI
                                                                                                          scrFI
                                                                                                          mvaI      mnlI
                                                                                                          ecoRII
                                                                                                          dsaV
          nlaIII                                                                                          bstNI     ecoNI
      sau3AI                                                                                              apyI[dcm+]       mnlI
      mboI/ndeII[dam-]                            maeII                                       mnlI       bsaJI     bslI ddeI
      dpnI[dam+]                                 aflIII
      dpnII[dam-]
 maeIII alwI[dam-]  apoI       maeIII
901 GTGACAAGGA TCATGCAGGA ATTTGAAAGT GACACGTTTT TCCCAGAAAT TGATTTGGGG AAATATAAAC CTCTCCCAGA ATACCCAGGC GTCCTCTCTG
    CACTGTTCCT AGTACGTCCT TAAACTTTCA CTGTGCAAAA AGGGTCTTTA ACTAAACCCC TTTATATTTG GAGAGGGTCT TATGGGTCCG CAGGAGAGAC

     scrFI
     mvaI
     ecoRII
     dsaV
     bstNI
     apyI[dcm+]
   sau96I                                                                    sfaNI
   avaII                                                                       mboII                    mnlI      aluI
   asuI   mnlI        sfaNI                    accI       mboII
1001 AGGTCCAGGA GGAAAAAGGC ATCAAGTATA AGTTTGAAGT CTACGAGAAG AAAGACTAAC AGGAAGATGC TTTCAAGTTC TCTGCTCCCC TCCTAAAGCT
     TCCAGGTCCT CCTTTTTCCG TAGTTCATAT TCAAACTTCA GATGCTCTTC TTTCTGATTG TCCTTCTACG AAAGTTCAAG AGACGAGGGG AGGATTTCGA
                                                                  ^END DHFR

                                                 styI
                                                 bsaJI
                                             sau3AI
                                             mboI/ndeII[dam-]
                  nlaIII                     dpnI[dam+]                   aluI
                 styI                        dpnII[dam-]                fnu4HI      tru9I
                 ncoI                        alwI[dam-]                 bsoFI       mseI
  ppu10I         dsaI bsmFI                  bstYI/xhoII                bbvI      aseI/asnI/vspI
  nsiI/avaIII    bsaJI           cac8I
1101 ATGCATTTTT ATAAGACCAT GGGACTTTTG CTGGCTTTAG ATCCCCTTGG CTTCGTTAGA ACGCAGCTAC AATTAATACA TAACCTTATG TATCATACAC
     TACGTAAAAA TATTCTGGTA CCCTGAAAAC GACCGAAATC TAGGGGAACC GAAGCAATCT TGCGTCGATG TTAATTATGT ATTGGAATAC ATAGTATGTG
                                                                        sau96I
                                                                        avaII
                                                                        asuI
                                                                      scrFI
                                                                      mvaI
                                                                      ecoRII
```

FIG. 48D

```
                                                                             dsaV                          ecoRI
                                                                             bstNI                        taqI   apoI
                                                                             apyI[dcm+]        mnlI       claI/bsp106
            maeIII                                                    bslI  bsaJI              bsaJI      bspDI[dam-]
           hphI    scfI       fokI
1201 ATACGATTTA GGTGACACTA TAGATAACAT CCACTTTGCC TTTCTCTCCA CAGGTGTCCA CTCCCAGGTC CAACTGCACC TCGGTTCTAT CGATTGAATT
     TATGCTAAAT CCACTGTGAT ATCTATTGTA GGTGAAACGG AAAGAGAGGT GTCCACAGGT GAGGGTCCAG GTTGACGTGG AGCCAAGATA GCTAACTTAA
                                                                    seq from pRK6G425VH: Cla-AvrII^

                                                                                                       scrFI
                                                                                                       mvaI  fnu4HI
                                                                                                       ecoRII
                                                                                                       dsaV
    nlaIII                                                                                             bstNI bsoFI
    styI                                                                                               apyI[dcm+]
    pflMI                                                                            rmaI                    bbvI
    ncoI                                   rmaI                rsaI                  maeI         haeI
    dsaI                                   maeI          bpmI/gsuI[dcm-]             bfaI     aciI haeIII/palI
    bslI fokI                              bfaI         bsrI    csp6I             aluI
    bsaJI        nlaIII    fokI
1301 CCACCATGGG ATGGTCATGT ATCATCCTTT TTCTAGTAGC AACTGCAACT GGAGTACATT CAGAAGTTCA GCTAGTGCAG TCTGGCGGTG GCCTGGTGCA
     GGTGGTACCC TACCAGTACA TAGTAGGAAA AAGATCATCG TTGACGTTGA CCTCATGTAA GTCTTCAAGT CGATCACGTC AGACCGCCAC CGGACCACGT
                                                                        E  V  Q   L  V  Q   S  G  G  G   L  V  Q
   1

                                                                                          scrFI
                                                                                          nciI
                                                                                          mspI
                                                                                          hpaII
                                                                                          dsaV
                                                                                          cauII
                                                                                          xmaI/pspAI
                                                                                          smaI
                                                                                          scrFI
                                                                                          nciI
                                                                                          dsaV            scrFI
                                                                                          cauII           mvaI
                                                                                          bslI            ecoRII
                                                                                          bsaJI           dsaV
      hgiJII                                                                       avaI          bstNI
      bsp1286                                                                           bsaJI          bslI
      bmyI                                                  pleI                                   apyI[dcm+]
   scrFI                                                 hinfI               sau96I    sau96I       haeIII/palI
   mvaI banII                 aluI                     taqI                  avaII     nlaIV    haeIII/palI  sau96I
   ecoRII                   alwNI[dcm-]                    xhoI                   asuI          asuI bslI  eco0109I/draII
   dsaV                         fnu4HI                     paeR7I                nlaIV      eco0109I/draII asuI
   bstNI                        bsoFI                      avaI  maeIII       bsrI
   bsaJI                        bbvI
   apyI[dcm+]
1401 GCCAGGGGGC TCACTCCGTT TGTCCTGTGC AGCTTCTGGC TACTCCTTCT CGAGTCACTA TATGCACTGG GTCCGTCAGG CCCCGGGTAA GGGCCTGGAA
     CGGTCCCCCG AGTGAGGCAA ACAGGACACG TCGAAGACCG ATGAGGAAGA GCTCAGTGAT ATACGTGACC CAGGCAGTCC GGGGCCCATT CCCGGACCTT
  14  P  G  G   S  L  R  L   S  C  A   A  S  G   Y  S  F  S   S  H  Y   M  H  W   V  R  Q  A   P  G  K   G  L  E
```

FIG. 48E

```
                   bslI                                                                      thaI
                 sau3AI                                                                      fnuDII/mvnI
                 mboI/ndeII[dam-]                                     haeIII/palI            bstUI
                 dpnI[dam+]                maeII                     sau96I                  bsh1236I
                 dpnII[dam-]              snaBI                      asuI                   nruI
                 alwI[dam-]     hphI      bsaAI
1501 TGGGTTGGAT ATATTGATCC TTCCAATGGT GAAACTACGT ATAATCAAAA GTTCAAGGGC CGTTTCACTT TATCTCGCGA CAACTCCAAA AACACAGCAT
     ACCCAACCTA TATAACTAGG AAGGTTACCA CTTTGATGCA TATTAGTTTT CAAGTTCCCG GCAAAGTGAA ATAGAGCGCT GTTGAGGTTT TTGTGTCGTA
  47 W  V  G  Y   I  D  P   S  N  G   E  T  T  Y   N  Q  K   F  K  G   R  F  T  L   S  R  D   N  S  K   N  T  A  Y

                                                                                                        hinlI/acyI
                                                                                                        ahaII/bsaHI
                                                                                        bsrI            aatII
  scfI                                                                                maeIII          taqI
  pstI                cac8I   mnlI                                 mnlI               hphI         mboII   maeII
  bsgI              cac8I   ddeI drdI
 bspMI
1601 ACCTGCAGAT GAACAGCCTG CGTGCTGAGG ACACTGCCGT CTATTACTGT GCAAGAGGGG ATTATCGCTA CAATGGTGAC TGGTTCTTCG ACGTCTGGGG
     TGGACGTCTA CTTGTCGGAC GCACGACTCC TGTGACGGCA GATAATGACA CGTTCTCCCC TAATAGCGAT GTTACCACTG ACCAAGAAGC TGCAGACCCC
  81  L  Q  M   N  S  L   R  A  E  D   T  A  V   Y  Y  C   A  R  G  D   Y  R  Y   N  G  D   W  F  F  D   V  W  G

                                                                                                          scrFI
                                        sau96I                                                            mvaI
                                       sau96I                                                             ecoRII
                                       nlaIV                                                              dsaV
                                       hgiJII                        nlaIV                                bstNI
                                       bsp1286                       hgiCI                           bsaJI
                   esp3I             bsp120I                       banI                              sau96I
        scrFI                            bmyI                        scrFI                           haeIII/palI
        mvaI        bsmBI            banII                       mvaI                              asuI
        ecoRII                       asuI              mboII    ecoRII                                 fnu4HI
        dsaV                                                 bpuAI     dsaV              hgiAI/aspHI            bsoFI
        bstNI hphI         mnlI              apaI      haeIII/palI    bstNI       bseRI   bsp1286   bsp1286 aciI bsaJI
        apyI[dcm+]         bsaJI         styI   bsaJI asuI    bbsI    apyI[dcm+]  mnlI   bsiHKAI   bmyI  nspBII apyI[dcm+]
       bsaJI maeIII      bseRI    mnlI  haeIII/palI eco0109I/draII   bsaJI     mnlI     bmyI   mnlI
     nlaIV    bstEII bsmAI
1701 TCAAGGAACC CTGGTCACCG TCTCCTCGGC CTCCACCAAG GGCCCATCGG TCTTCCCCCT GGCACCCTCC TCCAAGAGCA CCTCTGGGGG CACAGCGGCC
     AGTTCCTTGG GACCAGTGGC AGAGGAGCCG GAGGTGGTTC CCGGGTAGCC AGAAGGGGGA CCGTGGGAGG AGGTTCTCGT GGAGACCCCC GTGTCGCCGG
 114  Q  G  T   L  V  T  V   S  S  A   S  T  K   G  P  S  V   F  P  L   A  P  S   S  K  S  T   S  G  G   T  A  A
```

FIG. 48F

```
     scrFI
     mvaI
     ecoRII
     ecoNI
     dsaV
     bstNI
     bslI
     apyI[dcm+]
    fnu4HI                             maeIII                          nlaIV    hinPI
    bsoFI                                hphI                          kasI      narI        hgiAI/aspHI
    bbvI                                mspI                                     hinlI/acyI      bsp1286
                                        hpaII                                    hgiCI     bsiHKAI
                                       cfr10I/bsrFI                              haeII        bmyI         mspI
                                       bsaWI                                     banI        cac8I         hpaII
                               bslI    ageI   tth111I/aspI                       ahaII/bsaHI fnu4HI        scrFI
                                                                             ddeI hhaI/cfoI  bsoFI         nciI
                                                                                   nspBII    aciI apaLI/snoI dsaV
                                                                                             alw44I/snoI   cauII    scfI
1801 CTGGGCTGCC TGGTCAAGGA CTACTTCCCC GAACCGGTGA CGGTGTCGTG GAACTCAGGC GCCCTGACCA GCGGCGTGCA CACCTTCCCG GCTGTCCTAC
     GACCCGACGG ACCAGTTCCT GATGAAGGGG CTTGGCCACT GCCACAGCAC CTTGAGTCCG CGGGACTGGT CGCCGCACGT GTGGAAGGGC CGACAGGATG
147  L  G  C  L   V  K  D   Y  F  P   E  P  V  T   V  S  W   N  S  G   A  L  T  S   G  V  H   T  F  P   A  V  L  Q

                                                         fnu4HI
                                                         bsoFI     nlaIV
                                                        rmaI       hgiCI
  ddeI pleI          fnu4HI              bsp1286 maeI              banI                          tfiI
  mnlI  hinfI        bsoFI          maeIII       bfaI   aluI bsp1286                             hinfI
  eco81I       mnlI  bbvI           hphI   bmyI mnlI  bbvI  bmyI                            maeII
  bsu36I/mstII/sauI  ddeI
1901 AGTCCTCAGG ACTCTACTCC CTCAGCAGCG TGGTGACTGT GCCCTCTAGC AGCTTGGGCA CCCAGACCTA CATCTGCAAC GTGAATCACA AGCCCAGCAA
     TCAGGAGTCC TGAGATGAGG GAGTCGTCGC ACCACTGACA CGGGAGATCG TCGAACCCGT GGGTCTGGAT GTAGACGTTG CACTTAGTGT TCGGGTCGTT
181   S  S  G   L  Y  S   L  S  S  V   V  T  V   P  S  S   S  L  G  T   Q  T  Y   I  C  N   V  N  H  K   P  S  N

                                                                                           ahdI/eam1105I
                                                                                           sau96I
                                                                                           avaII
                                                                                      scrFI
                                                                                      mvaI     asuI
                                                                                      ecoRII
                                                                                      dsaV
                    hgiJII                                nlaIII                      bstNI  nlaIV      mboII
    styI            bsp1286                             nspI          bsp1286         bsaJI  bsmFI      bpuAI
    bsaJI           bmyI                  maeIII        nspHI         bmyI alwNI[dcm-] apyI[dcm+]       bbsI mnlI
    mslI            banII
2001 CACCAAGGTG GACAAGAAAG TTGAGCCCAA ATCTTGTGAC AAAACTCACA CATGCCCACC GTGCCCAGCA CCTGAACTCC TGGGGGGACC GTCAGTCTTC
     GTGGTTCCAC CTGTTCTTTC AACTCGGGTT TAGAACACTG TTTTGAGTGT GTACGGGTGG CACGGGTCGT GGACTTGAGG ACCCCCCTGG CAGTCAGAAG
214   T  K  V   D  K  K  V   E  P  K   S  C  D   K  T  H  T   C  P  P   C  P  A   P  E  L  L   G  G  P   S  V  F
```

FIG. 48G

```
                                           sau96I
                                           nlaIV
                                         mspI
                                         hpaII
                                        scrFI
                                        nciI
                                        dsaV
                                    sau3AI   avaII                nlaIII
                                    mboI/ndeII[dam-]             nspI                              drdI   mnlI
                                 nlaIII   cauII       mnlI       nspHI                           mboII  ddeI
                                rcaI dpnI[dam+]      ddeI       mslI                             bpuAI eco81I
                              mnlI   dpnII[dam-]    eco81I maeIII                   maeII       bbsI  bsu36I/mstII/sauI
   mboII              styI  mslI bspHI[dam-]   asuI bsu36I/mstII/sauI  GTGGTGGTGG ACGTGAGCCA CGAAGACCCT GAGGTCAAGT
  earI/ksp632I        bsaJI GGACACCCTC ATGATCTCCC GGACCCCTGA GGTCACATGC CACCACCACC TGCACTCGGT GCTTCTGGGA CTCCAGTTCA
2101 CTCTTCCCCC CAAAACCCAA CCTGTGGGAG TACTAGAGGG CCTGGGGACT CCAGTGTACG  V  V  V  D   V  S  H   E  D  P   E  V  K  F
     GAGAAGGGGG GTTTTGGGTT  D  T  L   M  I  S  R   T  P  E   V  T  C
247  L  F  P  P   K  P  K

                                                   aciI
                                                   thaI
                                                   fnuDII/mvnI
                                                   bstUI
                                                   bsh1236I
                                                   sacII/sstII
                                                   nspBII
                                                   kspI
                                                   dsaI
                                                   bsaJI                         rsaI
        maeII                                      aciI                          csp6I
       rsaI                                        fnu4HI  mnlI      rsaI      maeII                   hphI
       csp6I                                       bsoFI   bseRI     csp6I     bsaAI         hgaI mnlI
    bsrI bsaAI             mnlI                                                CACGTACCGT GTGGTCAGCG TCCTCACCGT
2201 TCAACTGGTA CGTGGACGGC GTGGAGGTGC ATAATGCCAA GACAAAGCCG CGGGAGGAGC AGTACAACAG GTGCATGGCA CACCAGTCGC AGGAGTGGCA
     AGTTGACCAT GCACCTGCCG CACCTCCACG TATTACGGTT CTGTTTCGGC GCCCTCCTCG TCATGTTGTC  T  Y  R   V  V  S  V   L  T  V
281   N  W  Y   V  D  G   V  E  V  H   N  A  K   T  K  P   R  E  E  Q   Y  N  S

     scrFI
     mvaI
     ecoRII                                                                                          fnu4HI
     dsaV                                                                                                 bsoFI
 ecoNI bstNI bsrI                  rsaI       bsmAI                                                       bbvI
 bslI  apyI[dcm+]                  csp6I       bsaI          mnlI                 taqI
2301 CCTGCACCAG GACTGGCTGA ATGGCAAGGA GTACAAGTGC AAGGTCTCCA ACAAAGCCCT CCCAGCCCCC ATCGAGAAAA CCATCTCCAA AGCCAAAGGG
     GGACGTGGTC CTGACCGACT TACCGTTCCT CATGTTCACG TTCCAGAGGT TGTTTCGGGA GGGTCGGGGG TAGCTCTTTT GGTAGAGGTT TCGGTTTCCC
314   L  H  Q   D  W  L  N   G  K  E   Y  K  C   K  V  S  N   K  A  L   P  A  P   I  E  K  T   I  S  K   A  K  G
```

FIG. 48H

```
                                     scrFI
                                     nciI
                                     mspI
                                     hpaII
                                     dsaV
                                     cauII
                                    xmaI/pspAI
                                    smaI
                                    scrFI                          scrFI        scrFI
                                    nciI                           mvaI             mvaI
                                    dsaV                           ecoRII       ecoRII
                                    cauII                          dsaV         dsaV
                         rsaI     fokI                             bstNI            bstNI
                         csp6I  bslI  bsaJI mboII                  apyI[dcm+]       apyI[dcm+]
      avaI             bsp1407I/bsrGI bslI avaI  earI/ksp632I     sexAI         bspMI
2401 CAGCCCCGAG AACCACAGGT GTACACCCTG CCCCCATCCC GGGAAGAGAT GACCAAGAAC CAGGTCAGCC TGACCTGCCT GGTCAAAGGC TTCTATCCCA
     GTCGGGGCTC TTGGTGTCCA CATGTGGGAC GGGGGTAGGG CCCTTCTCTA CTGGTTCTTG GTCCAGTCGG ACTGGACGGA CCAGTTTCCG AAGATAGGGT
347 Q  P  R  E   P  Q  V   Y  T  L   P  P  S  R   E  E  M   T  K  N   Q  V  S  L   T  C  L   V  K  G   F  Y  P  S

                                   mspI
                                   hpaII
        dsaI                     fnu4HI                                                              mnlI
        bslI                     bsoFI                                         pleI                      
    msII bsaJI            bsrDI  bbvI                              mnlI        hinfI     nlaIV  mboII  scfI cac8I
2501 GCGACATCGC CGTGGAGTGG GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACGC CTCCCGTGCT GGACTCCGAC GGCTCCTTCT TCCTCTACAG
     CGCTGTAGCG GCACCTCACC CTCTCGTTAC CCGTCGGCCT CTTGTTGATG TTCTGGTGCG GAGGGCACGA CCTGAGGCTG CCGAGGAAGA AGGAGATGTC
381  D  I  A   V  E  W   E  S  N  G   Q  P  E   N  N  Y   K  T  T  P   P  V  L   D  S  D   G  S  F  F   L  Y  S

                                        mboII
                                       bpuAI                   nlaIII
                                     maeII                   ppu10I                                      sapI
        dsaI                 fnu4HI  xmnI bbsI               nsiI/avaIII                                 mboII mnlI
      hphI                   bsoFI   asp700        nlaIII    sfaNI   mnlI                                earI/ksp632I
    aluI  bsaJI       bspMI  bbvI
2601 CAAGCTCACC GTGGACAAGA GCAGGTGGCA GCAGGGGAAC GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCTC
     GTTCGAGTGG CACCTGTTCT CGTCCACCGT CGTCCCCTTG CAGAAGAGTA CGAGGCACTA CGTACTCCGA GACGTGTTGG TGATGTGCGT CTTCTCGGAG
414  K  L  T   V  D  K  S   R  W  Q   Q  G  N   V  F  S  C   S  V  M   H  E  A   L  H  N  H   Y  T  Q   K  S  L
```

FIG. 48I

```
                                                                                                sau96I
                                                                                       aciI     haeIII/palI
                                                               taqI                    fnu4HI   asuI
                 scrFI                                     pleI                        bsoFI nlaIII
                 nciI                                   rmaI salI   scfI               sfiI  styI
                 mspI                                   maeI hincII/hindII            eaeI   ncoI             aluI
                 hpaII                             sau96I  hinfI    pstI              cfrI   dsaI            fnu4HI
                 dsaV                              haeIII/palI      bsgI          aluI haeIII/palI           bsoFI
             bsmAI                                 asuI bfaI accI bspMI          hindIII bglI bsaJI          bbvI        maeIII
          bslI   cauII
2701 TCCCTGTCTC CGGGTAAATG AGTGCGACGG CCCTAGAGTC GACCTGCAGA AGCTTGGCCG CCATGGCCCA ACTTGTTTAT TGCAGCTTAT AATGGTTACA
     AGGGACAGAG GCCCATTTAC TCACGCTGCC GGGATCTCAG CTGGACGTCT TCGAACCGGC GGTACCGGGT TGAACAAATA ACGTCGAATA TTACCAATGT
 447 S  L  S  P   G  K  O (SEQ ID NO.71)

                                                                 rmaI
                                                                 maeI                                  nlaIII alwI[dam-]
                 sfaNI   apoI                               bsmI bfaI
2801 AATAAAGCAA TAGCATCACA AATTTCACAA ATAAAGCATT TTTTTCACTG CATTCTAGTT GTGGTTTGTC CAAACTCATC AATGTATCTT ATCATGTCTG
     TTATTTCGTT ATCGTAGTGT TTAAAGTGTT TATTTCGTAA AAAAAGTGAC GTAAGATCAA CACCAAACAG GTTTGAGTAG TTACATAGAA TAGTACAGAC

       sau3AI
       mboI/ndeII[dam-]
       dpnI[dam+]
       dpnII[dam-]
      pvuI/bspCI
      mcrI
      bsiEI                                                                        rsaI
     taqI[dam-]  tru9I                                                             csp6I
    claI/bsp106[dam-]       fnu4HI    haeI                                        nlaIV
    bspDI[dam-]  mseI       bsoFI styI                                            kpnI
   sau3AI     xmnI          bbvI  ncoI                                            hgiCI
   mboI/ndeII[dam-]       hinPI   dsaI haeIII/palI                                banI
   dpnI[dam+] asp700      hhaI/cfoI nlaIII                                        asp718     mnlI
   dpnII[dam-]  aseI/asnI/vspI   bsaJI            mnlI       mnlI                 acc65I   ddeI  aciI
2901 GATCGATCGG GAATTAATTC GGCGCAGCAC CATGGCCTGA AATAACCTCT GAAAGAGGAA CTTGGTTAGG TACCTTCTGA GGCGGAAAGA ACCATCTGTG
     CTAGCTAGCC CTTAATTAAG CCGCGTCGTG GTACCGGACT TTATTGGAGA CTTTCTCCTT GAACCAATCC ATGGAAGACT CCGCCTTTCT TGGTAGACAC
```

FIG. 48J

```
                                                 scrFI                                                  sfaNI
                                                 mvaI                                                       ppu10I                             scrFI
                                                 ecoRII                                                 nsiI/avaIII                     mvaI
                                                 dsaV                                                   nlaIII                          ecoRII
                                                 bstNI                                                      sphI                              dsaV
                                                 apyI[dcm+]                                                 nspI                              bstNI
                                                bsaJI                                                       nspHI                             apyI[dcm+]
                                            bsmFI   nlaIV      cac8I                                        cac8I                            sexAI          bsmFI
3001 GAATGTGTGT CAGTTAGGGT GTGGAAAGTC CCCAGGCTCC CCAGCAGGCA GAAGTATGCA AAGCATGCAT CTCAATTAGT CAGCAACCAG GTGTGGAAAG
     CTTACACACA GTCAATCCCA CACCTTTCAG GGGTCCGAGG GGTCGTCCGT CTTCATACGT TTCGTACGTA GAGTTAATCA GTCGTTGGTC CACACCTTTC

         nlaIV                                   sfaNI
       scrFI                             ppu10I
       mvaI                                    nsiI/avaIII
       ecoRII                           nlaIII
       dsaV                            sphI
       bstNI                                 nspI                                                       aciI
       apyI[dcm+]                            nspHI                                  aciI                   aciI  fokI            aciI
      bsaJI         cac8I                    cac8I                                bsmFI
3101 TCCCCAGGCT CCCCAGCAGG CAGAAGTATG CAAAGCATGC ATCTCAATTA GTCAGCAACC ATAGTCCCGC CCCTAACTCC GCCCATCCCG CCCCTAACTC
     AGGGGTCCGA GGGGTCGTCC GTCTTCATAC GTTTCGTACG TAGAGTTAAT CAGTCGTTGG TATCAGGGCG GGGATTGAGG CGGGTAGGGC GGGGATTGAG

                                                                                     fnu4HI
                                                                                     bsoFI
                                                                                     bglI
                                                                                    sfiI
                                  nlaIII                                            haeIII/palI
                                 styI                                             mnlI     mnlI        ddeI
                                 ncoI                                          haeIII/palI bsaJI  mnlI    aluI                mnlI
                            bslI dsaI                                                          haeIII/palI                    bseRI
        bsrI   aciI         aciI bsaJI                                       mnlI bsaJI aciI
3201 CGCCCAGTTC CGCCCATTCT CCGCCCCATG GCTGACTAAT TTTTTTTATT TATGCAGAGG CCGAGGCCGC CTCGGCCTCT GAGCTATTCC AGAAGTAGTG
     GCGGGTCAAG GCGGGTAAGA GGCGGGGTAC CGACTGATTA AAAAAAATAA ATACGTCTCC GGCTCCGGCG GAGCCGGAGA CTCGATAAGG TCTTCATCAC
```

FIG. 48K

```
                                                  scrFI
                                                  nciI
                                                  mspI
                                                  hpaII
                        rmaI                      dsaV
                        maeI                    haeIII/palI
                       styI                                          tfiI
                       bsaJI               aluI mcrI                 hinfI
                       blnI              rmaI   eagI/xmaIII/eclXI  aciI
                       avrII[dam-]       maeI   eaeI               thaI
                     haeIII/palI         bfaI   cfrI               fnuDII/mvnI
                    stuI                nheI    bsiEI              bstUI           pleI
                    haeI                cac8I  mspI cauII          bsh1236I        hinfI
      mnlI         mnlI bfaI           aluI    hpaII
3301 AGGAGGCTTT TTTGGAGGCC TAGGCTTTTG CAAAAAGCTA GCTTATCCGG CCGGGAACGG TGCATTGGAA CGCGGATTCC CCGTGCCAAG AGTCAGGTAA
     TCCTCCGAAA AAACCTCCGG ATCCGAAAAC GTTTTTCGAT CGAATAGGCC GGCCCTTGCC ACGTAACCTT GCGCCTAAGG GGCACGGTTC TCAGTCCATT
                      ^seq from pSVI6B5-6G4VL: AvrII - HindIII frag                U1 matched splice donar^

                                                                                       sau3AI
                                                                                       mboI/ndeII[dam-]
                                                                                       dpnI[dam+]
                                                                                       dpnII[dam-]
                                                                                       alwI[dam-]
                                                                                     taqI[dam-]
                                                                                    claI/bsp106[dam-]
                                                 fnu4HI                             bspDI[dam-]
                                                 bsoFI                             sau3AI
                                                 aciI                              mboI/ndeII[dam-]
                              bstXI             thaI                               dpnI[dam+]
       aciI          scfI  sau96I    styI       fnuDII/mvnI tru9I                  dpnII[dam-]
     rsaI        pleI      haeIII/palI          bstUI       mseI                  alwI[dam-]           fokI
     csp6I  scfI hinfI     asuI      bsaJI      bsh1236I   aseI/asnI/vspI
3401 GTACCGCCTA TAGAGTCTAT AGGCCCACCC CCTTGGCTTC GTTAGAACGC GGCTACAATT AATACATAAC CTTTTGGATC GATCCTACTG ACACTGACAT
     CATGGCGGAT ATCTCAGATA TCCGGGTGGG GGAACCGAAG CAATCTTGCG CCGATGTTAA TTATGTATTG GAAAACCTAG CTAGGATGAC TGTGACTGTA
                                          ^sp6 promoter                          ^removed ATG
                                                                                          ^U2 match
                                                                                    lariat consensus^
                                                                         IgG vH natural lariat restored^
```

FIG. 48L

```
                              sau96I
                              avaII
                              asuI
                           scrFI
                           mvaI
                           ecoRII
                           dsaV
                           bstNI
                           apyI[dcm+]
                     bslI  bsaJI
                                                        rmaI
                                                  maeI
                                                        bfaI
                                             thaI    nheI
                                             fnuDII/mvnI
                                                   bstUI  cac8I
                                        mnlI       bsh1236I  aluI
                                        bsaJI    nruI    aluI
                                                                    claI/bsp106
                                                                  sfaNI
                                                                     fnu4HI
                                                                     bsoFI taqI
                                                                     bbvI bspDI[dam-]
                                                                                  nlaIII
                                                                                       styI
                                                                                 pflMI
                                                                                 ncoI
                                                                              ecoRI     dsaI
                                                                              apoI      bslI fokI
                                                                                        bsaJI
3501 CCACTTTTTC TTTTTCTCCA CAGGTGTCCA CTCCCAGGTC CAACTGCACC TCGGTTCGCG AAGCTAGCTT GGGCTGCATC GATTGAATTC CACCATGGGA
     GGTGAAAAAG AAAAAGAGGT GTCCACAGGT GAGGGTCCAG GTTGACGTGG AGCCAAGCGC TTCGATCGAA CCCGACGTAG CTAACTTAAG GTGGTACCCT
                                                  ^cloning linker

                                                                       aluI
                                                                      sstI
                                                                      sacI
                                                                      hgiJII
                                                                      hgiAI/aspHI
                                                                      ecl136II
                                                                      bsp1286
                                                                      bsiHKAI
                                                                 bsmFI bmyI
                                     rsaI                       bsrI   avaI
                         rmaI                                                          mnlI
                         maeI      bpmI/gsuI[dcm-]
                         bfaI     bsrI   csp6I    ecoRV        tth111I/aspI banII   aciI
       nlaIII   fokI
3601 TGGTCATGTA TCATCCTTTT TCTAGTAGCA ACTGCAACTG GAGTACATTC AGATATCCAG ATGACCCAGT CCCCGAGCTC CCTGTCCGCC TCTGTGGGCG
     ACCAGTACAT AGTAGGAAAA AGATCATCGT TGACGTTGAC CTCATGTAAG TCTATAGGTC TACTGGGTCA GGGGCTCGAG GGACAGGCGG AGACACCCGC
   1                                                        D  I  Q  M  T  Q  S   P  S  S  L  S  A   S  V  G  D

                       scfI
                       pstI
                       bsgI
                      sse8387I
        hphI                                                                                 scrFI
       maeIII          bspMI                                                                 mvaI
      bstEII     hphI    bspMI                                                               ecoRII
                                            rsaI                                             dsaV
                                     ddeI                    maeII                           bstNI     aluI
                                   aluI  csp6I               snaBI                           apyI[dcm+]
                                  hindIII   nlaIII           bsaAI     bsrI
3701 ATAGGGTCAC CATCACCTGC AGGTCAAGTC AAAGCTTAGT ACATGGTATA GGTGCTACGT ATTTACACTG GTATCAACAG AAACCAGGAA AAGCTCCGAA
     TATCCCAGTG GTAGTGGACG TCCAGTTCAG TTTCGAATCA TGTACCATAT CCACGATGCA TAAATGTGAC CATAGTTGTC TTTGGTCCTT TTCGAGGCTT
  18  R  V  T   I  T  C   R  S  S  Q   S  L  V   H  G  I   G  A  T  Y   L  H  W   Y  Q  Q   K  P  G  K   A  P  K
```

FIG. 48M

```
                                                     mspI
                                                     hpaII
                                                     bslI
                                                    bsaWI
                                                   sau3AI
                                                   mboI/ndeII[dam-]
                                                   dpnI[dam+]
                                                   dpnII[dam-]
                                                   alwI[dam-]
                  tfiI                            nlaIV
                  hinfI        bsmFI              bstYI/xhoII                                  fnu4HI
                 taqI        bpmI/gsuI[dcm-]      bamHI                                        bsoFI
                claI/bsp106    pleI               alwI[dam-]   bsmFI                           bbvI
                bspDI[dam-]    hinfI                                                          scfI
                                                                                              pstI
                                                                                              bsgI
3801 ACTACTGATT TACAAAGTAT CCAATCGATT CTCTGGAGTC CCTTCTCGCT TCTCTGGATC CGGTTCTGGG ACGGATTTCA CTCTGACCAT CAGCAGTCTG
     TGATGACTAA ATGTTTCATA GGTTAGCTAA GAGACCTCAG GGAAGAGCGA AGAGACCTAG GCCAAGACCC TGCCTAAAGT GAGACTGGTA GTCGTCAGAC
  51  L  L  I   Y  K  V  S   N  R  F   S  G  V   P  S  R  F   S  G  S   G  S  G   T  D  F  T   L  T  I   S  S  L

                                                                        rsaI
                                                                        csp6I
                                                                       nlaIV
                                                                       kpnI styI
                                           bsrBI                       hgiCI          sau3AI
                                           aciI                        banI bsaJI     mboI/ndeII[dam-] fnu4HI
      mboII                       rsaI    bsmFI                        asp718         dpnI[dam+]       bsoFI
      bpuAI                       csp6I  nlaIII          maeII          acc65I         dpnII[dam-]      bbvI
      bbsI                        scaI
3901 CAGCCAGAAG ACTTCGCAAC TTATTACTGT TCACAGAGTA CTCATGTCCC GCTCACGTTT GGACAGGGTA CCAAGGTGGA GATCAAACGA ACTGTGGCTG
     GTCGGTCTTC TGAAGCGTTG AATAATGACA AGTGTCTCAT GAGTACAGGG CGAGTGCAAA CCTGTCCCAT GGTTCCACCT CTAGTTTGCT TGACACCGAC
  84 Q  P  E  D   F  A  T   Y  Y  C   S  Q  S  T   H  V  P   L  T  F   G  Q  G  T   K  V  E   I  K  R   T  V  A  A

                                                                                                       haeIII/palI
                                                        xmnI                       xmnI               haeI
       mboII                                            asp700              cac8I  asp700            mnlI
       bpuAI
       bbsI    mboII aciI
4001 CACCATCTGT CTTCATCTTC CCGCCATCTG ATGAGCAGTT GAAATCTGGA ACTGCTTCTG TTGTGTGCCT GCTGAATAAC TTCTATCCCA GAGAGGCCAA
     GTGGTAGACA GAAGTAGAAG GGCGGTAGAC TACTCGTCAA CTTTAGACCT TGACGAAGAC AACACACGGA CGACTTATTG AAGATAGGGT CTCTCCGGTT
 118   P  S  V   F  I  F   P  P  S  D   E  Q  L   K  S  G   T  A  S  V   V  C  L   L  N  N   F  Y  P  R   E  A  K
```

FIG. 48N

```
                                             scrFI
                                             mvaI
                                             ecoRII
                                             dsaV
                                             bstNI                                                                              fnu4HI
                                             apyI[dcm+]                                                               ddeI    bsoFI
      rsaI                     mnlI                      maeIII                                             scfI     mnlI    bbvI
      csp6I                    bslI         maeIII bsaJI
4101 AGTACAGTGG AAGGTGGATA ACGCCCTCCA ATCGGGTAAC TCCCAGGAGA GTGTCACAGA GCAGGACAGC AAGGACAGCA CCTACAGCCT CAGCAGCACC
     TCATGTCACC TTCCACCTAT TGCGGGAGGT TAGCCCATTG AGGGTCCTCT CACAGTGTCT CGTCCTGTCG TTCCTGTCGT GGATGTCGGA GTCGTCGTGG
151   V  Q  W   K  V  D  N   A  L  Q   S  G  N   S  Q  E  S   V  T  E   Q  D  S   K  D  S  T   Y  S  L   S  S  T

                                                                                   sstI
                                                                                   sacI
                                                                                   hgiJII
                                                                                   hgiAI/aspHI
                                                                                   ecl136II
                                                                                   bsp1286
                                                                                   bsiHKAI
                                                                                   bmyI
                                                                                 ddeI cac8I
                                                                              haeIII/palI
                                                                             sau96I aluI
                                                                             asuI  banII
        ddeI                                                    hphI         eco0109I/draII
        celII/espI                                              maeIII       alwNI[dcm-]        maeIII     aluI
        blpI/bpu1102I                        accI     cac8I
     hgaI
4201 CTGACGCTGA GCAAAGCAGA CTACGAGAAA CACAAAGTCT ACGCCTGCGA AGTCACCCAT CAGGGCCTGA GCTCGCCCGT CACAAAGAGC TTCAACAGGG
     GACTGCGACT CGTTTCGTCT GATGCTCTTT GTGTTTCAGA TGCGGACGCT TCAGTGGGTA GTCCCGGACT CGAGCGGGCA GTGTTTCTCG AAGTTGTCCC
184  L  T  L  S   K  A  D   Y  E  K   H  K  V  Y   A  C  E   V  T  H   Q  G  L  S   S  P  V   T  K  S   F  N  R  G

                         sau96I
                  aciI   haeIII/palI
                  fnu4HI asuI
                  bsoFI nlaIII
                 sfiI  styI
              aluI haeIII/palI                       aluI
            hindIII bglI ncoI                        fnu4HI
          tru9I   eaeI   dsaI                        bsoFI
          mseI    cfrI   bsaJI                       bbvI         maeIII                  sfaNI  apoI
4301 GAGAGTGTTA AGCTTGGCCG CCATGGCCCA ACTTGTTTAT TGCAGCTTAT AATGGTTACA AATAAAGCAA TAGCATCACA AATTTCACAA ATAAAGCATT
     CTCTCACAAT TCGAACCGGC GGTACCGGGT TGAACAAATA ACGTCGAATA TTACCAATGT TTATTTCGTT ATCGTAGTGT TTAAAGTGTT TATTTCGTAA
218   E  C  o (SEQ ID NO.72)
```

FIG. 48O

```
                                                                                      sau3AI
                                                                                      mboI/ndeII[dam-]
                                                                                      dpnI[dam+]
                                                                                      dpnII[dam-]
                                                                                     pvuI/bspCI
                                                                                     mcrI
                                                                                     bsiEI
                                                                                    taqI[dam-]
                                                                                   claI/bsp106[dam-]
                                                                                   bspDI[dam-]  tru9I      fnu4HI    haeI
                                                                                  sau3AI        mseI       bsoFI styI
                                                                                  mboI/ndeII[dam-]         bbvI  ncoI
                    rmaI                                                          dpnI[dam+] xmnI        hinPI   dsaI haeIII/palI
                    maeI                                                          dpnII[dam-]  aseI/asnI/vspI    bsaJI
               bsmI bfaI                                                nlaIII alwI[dam-]   asp700     hhaI/cfoI nlaIII
4401 TTTTTCACTG CATTCTAGTT GTGGTTTGTC CAAACTCATC AATGTATCTT ATCATGTCTG GATCGATCGG GAATTAATTC GGCGCAGCAC CATGGCCTGA
     AAAAAGTGAC GTAAGATCAA CACCAAACAG GTTTGAGTAG TTACATAGAA TAGTACAGAC CTAGCTAGCC CTTAATTAAG CCGCGTCGTG GTACCGGACT
                                                                                  ^sv40 origin

                                                                                                                scrFI
                             rsaI                                                                               mvaI
                              csp6I                                                                             ecoRII
                             nlaIV                                                                              dsaV
                             kpnI                                                                               bstNI
                             hgiCI                                                                              apyI[dcm+]
                             banI                             aluI                                             bsaJI
                             asp718     mnlI                 pvuII                                         bsmFI   nlaIV
       mnlI      mnlI        acc65I   ddeI  aciI             nspBII
4501 AATAACCTCT GAAAGAGGAA CTTGGTTAGG TACCTTCTGA GGCGGAAAGA ACCAGCTGTG GAATGTGTGT CAGTTAGGGT GTGGAAAGTC CCCAGGCTCC
     TTATTGGAGA CTTTCTCCTT GAACCAATCC ATGGAAGACT CCGCCTTTCT TGGTCGACAC CTTACACACA GTCAATCCCA CACCTTTCAG GGGTCCGAGG

                          sfaNI                                           scrFI                                  sfaNI
                        ppu10I                                  mvaI                                            ppu10I
                        nsiI/avaIII            scrFI                                                            nsiI/avaIII
                       nlaIII                  mvaI                       ecoRII                          nlaIII
                      sphI                     ecoRII           dsaV                                           sphI
                      nspI                     dsaV             bstNI                                               nspI
                      nspHI                    bstNI                   apyI[dcm+]                                   nspHI
                      cac8I                    apyI[dcm+]             bsaJI                                         cac8I
       cac8I                                  sexAI                bsmFI   nlaIV      cac8I
4601 CCAGCAGGCA GAAGTATGCA AAGCATGCAT CTCAATTAGT CAGCAACCAG GTGTGGAAAG TCCCCAGGCT CCCCAGCAGG CAGAAGTATG CAAAGCATGC
     GGTCGTCCGT CTTCATACGT TTCGTACGTA GAGTTAATCA GTCGTTGGTC CACACCTTTC AGGGGTCCGA GGGGTCGTCC GTCTTCATAC GTTTCGTACG
```

FIG. 48P

```
                                                                                                         nlaIII
                                                                                                        styI
                                                                                                        ncoI
                                                                                                   bslI dsaI
                           aciI                    aciI                                            aciI bsaJI
                        bsmFI          aciI   fokI                aciI bsrI   aciI
4701 ATCTCAATTA GTCAGCAACC ATAGTCCCGC CCCTAACTCC GCCCATCCCG CCCCTAACTC CGCCCAGTTC CGCCCATTCT CCGCCCCATG GCTGACTAAT
     TAGAGTTAAT CAGTCGTTGG TATCAGGGCG GGGATTGAGG CGGGTAGGGC GGGGATTGAG GCGGGTCAAG GCGGGTAAGA GGCGGGGTAC CGACTGATTA

                                                                                             rmaI
                                                                                             maeI
                                                                                            styI
                          fnu4HI                                                            bsaJI
                          bsoFI                                                             blnI
                          bglI                                                              avrII[dam-]
                         sfiI                                                             haeIII/palI
                         haeIII/palI                                                     stuI
                       mnlI   mnlI      ddeI                           mnlI              haeI
                  haeIII/palI bsaJI  mnlI    aluI                  mnlI                 mnlI bfaI          aluI   maeIII
                mnlI bsaJI aciI   haeIII/palI                      bseRI
4801 TTTTTTTATT TATGCAGAGG CCGAGGCCGC CTCGGCCTCT GAGCTATTCC AGAAGTAGTG AGGAGGCTTT TTTGGAGGCC TAGGCTTTTG CAAAAAGCTG
     AAAAAAATAA ATACGTCTCC GGCTCCGGCG GAGCCGGAGA CTCGATAAGG TCTTCATCAC TCCTCCGAAA AAACCTCCGG ATCCGAAAAC GTTTTTCGAC
                                                                                                start pUC118^

              fnu4HI
             haeIII/palI       hinPI
            mcrI               hhaI/cfoI
            eagI/xmaIII/eclXI thaI
            eaeI               fnuDII/mvnI
          notI                 bstUI
        bsrBI bsoFI           hinPI            bspMI
      taqI  cfrI              hhaI/cfoI       scfI                                                            scrFI
     xhoI fnu4HI    tru9I     cac8I     tru9I  pstI                 haeIII/palI                               mvaI
     paeR7I bsiEI   pacI     ascI      ahaIII/draI                 eaeI                                       ecoRII
     avaI bsoFI     mseI tru9I bsh1236I mseI   bsgI  maeIII         cfrI                     bsrI             dsaV
    mnlI  aciI aciI     mseI bssHII   swaI    sse8387I     aluI    bsrI               maeII maeIII            bstNI
                                                                                                              apyI[dcm+]
                                                                                                             bsaJI
4901 TTACCTCGAG CGGCCGCTTA ATTAAGGCGC GCCATTTAAA TCCTGCAGGT AACAGCTTGG CACTGGCCGT CGTTTTACAA CGTCGTGACT GGGAAAACCC
     AATGGAGCTC GCCGGCGAAT TAATTCCGCG CGGTAAATTT AGGACGTCCA TTGTCGAACC GTGACCGGCA GCAAAATGTT GCAGCACTGA CCCTTTTGGG
      ^linearization linker inserted into HpaI site
```

FIG. 48Q

```
                                                                                                     sau3AI
                                                                                          sau96I     mboI/ndeII[dam-]
                                                                                          haeIII/palI dpnI[dam+]
                                                                cac8I                     asuI       dpnII[dam-]
                                           fnu4HI              aluI                     mnlI aciI  pvuI/bspCI
                         tru9I             bsoFI               pvuII                  mboII cac8I  mcrI
            maeIII       mseI              bbvI      fokI      nspBII                 earI/ksp632I bsiEI
                                                              cac8I
5001 TGGCGTTACC CAACTTAATC GCCTTGCAGC ACATCCCCCC TTCGCCAGCT GGCGTAATAG CGAAGAGGCC CGCACCGATC GCCCTTCCCA ACAGTTGCGT
     ACCGCAATGG GTTGAATTAG CGGAACGTCG TGTAGGGGGG AAGCGGTCGA CCGCATTATC GCTTCTCCGG GCGTGGCTAG CGGGAAGGGT TGTCAACGCA

                          hinPI
                          hhaI/cfoI
                         nlaIV                                                                                hinPI
                         narI                                                                                 thaI
                         kasI                                                                                 fnuDII/mvnI
                         hinlI/acyI                                                                           bstUI scfI
                         hgiCI                                                                                bsh1236I
                         haeII      aciI                                                                  rsaI hhaI/cfoI
                         banI    sfaNI                                                                    csp6I   bslI
        bglI             ahaII/bsaHI                   sfaNI      aciI          aciI     maeII
5101 AGCCTGAATG GCGAATGGCG CCTGATGCGG TATTTTCTCC TTACGCATCT GTGCGGTATT TCACACCGCA TACGTCAAAG CAACCATAGT ACGCGCCCTG
     TCGGACTTAC CGCTTACCGC GGACTACGCC ATAAAAGAGG AATGCGTAGA CACGCCATAA AGTGTGGCGT ATGCAGTTTC GTTGGTATCA TGCGCGGGAC

                            aciI
                         fnu4HI                     fnu4HI
                         bsoFI                      bsoFI
                        thaI                      hinPI                                  hinPI
                        fnuDII/mvnI               hhaI/cfoI                              hhaI/cfoI
          hinPI         bstUI                    thaI                                 rmaI
          hhaI/cfoI hinPI                        fnuDII/mvnI                     hinPI  haeII
       fnu4HI           hhaI/cfoI                bstUI                           hhaI/cfoI    bsrBI
       bsoFI      tru9I aciI                     bsh1236I     aciI               haeII maeI   aciI
       aciI       mseI bsh1236I              maeIII bbvI  maeIII           cac8I     bfaI  cac8I          mboII
5201 TAGCGGCGCA TTAAGCGCGG CGGGTGTGGT GGTTACGCGC AGCGTGACCG CTACACTTGC CAGCGCCCTA GCGCCCGCTC CTTTCGCTTT CTTCCCTTCC
     ATCGCCGCGT AATTCGCGCC GCCCACACCA CCAATGCGCG TCGCACTGGC GATGTGAACG GTCGCGGGAT CGCGGGCGAG GAAAGCGAAA GAAGGGAAGG
```

FIG. 48R

```
                 mspI                                     nlaIV
                 hpaII                                   hgiJII
                naeI                                     bsp1286                                   nlaIV
                cfr10I/bsrFI                             bmyI                                      hgiCI  taqI
           maeII  cac8I               aluI               banII          nlaIV                      banI mnlI
5301 TTTCTCGCCA CGTTCGCCGG CTTTCCCCGT CAAGCTCTAA ATCGGGGGCT CCCTTTAGGG TTCCGATTTA GTGCTTTACG GCACCTCGAC CCCAAAAAAC
     AAAGAGCGGT GCAAGCGGCC GAAAGGGGCA GTTCGAGATT TAGCCCCCGA GGGAAATCCC AAGGCTAAAT CACGAAATGC CGTGGAGCTG GGGTTTTTTG

                   maeII    haeIII/palI                                      maeII pleI              tru9I     pleI
                  draIII   sau96I                                           drdI   hinfI  maeII   mseI      hinfI
         hphI     bsaAI    asuI
5401 TTGATTTGGG TGATGGTTCA CGTAGTGGGC CATCGCCCTG ATAGACGGTT TTTCGCCCTT TGACGTTGGA GTCCACGTTC TTTAATAGTG GACTCTTGTT
     AACTAAACCC ACTACCAAGT GCATCACCCG GTAGCGGGAC TATCTGCCAA AAAGCGGGAA ACTGCAACCT CAGGTGCAAG AAATTATCAC CTGAGAACAA

                                                                                             tru9I
                       bslI                                                                  mseI          tru9I
       bsrI           bslI  avaI                                                haeIII/palI            aluI   mseI
5501 CCAAACTGGA ACAACACTCA ACCCTATCTC GGGCTATTCT TTTGATTTAT AAGGGATTTT GCCGATTTCG GCCTATTGGT TAAAAAATGA GCTGATTTAA
     GGTTTGACCT TGTTGTGAGT TGGGATAGAG CCCGATAAGA AAACTAAATA TTCCCTAAAA CGGCTAAAGC CGGATAACCA ATTTTTTACT CGACTAAATT

                                                                  hgiAI/aspHI
              thaI                                                bsp1286
              fnuDII/mvnI            maeII                        bsiHKAI                           aciI
          tru9I   apoI tru9I         psp1406I                     bmyI   ddeI                      fnu4HI
          mseI bstUI   mseI         tru9I                         apaLI/snoI  rsaI                 bsoFI      tru9I
       apoI    bsh1236I         sspI mseI                         alw44I/snoI csp6I             sfaNI         mseI        aciI
5601 CAAAAATTTA ACGCGAATTT TAACAAAATA TTAACGTTTA CAATTTTATG GTGCACTCTC AGTACAATCT GCTCTGATGC CGCATAGTTA AGCCAACTCC
     GTTTTTAAAT TGCGCTTAAA ATTGTTTTAT AATTGCAAAT GTTAAAATAC CACGTGAGAG TCATGTTAGA CGAGACTACG GCGTATCAAT TCGGTTGAGG

                                                                         hinPI                       sfaNI
                                                                         hhaI/cfoI                  mspI
                              hinPI                                     thaI                        hpaII
                             fnu4HI                                     fnuDII/mvnI                 scrFI
              maeIII         bsoFI                                      bstUI                       nciI
           maeII bsrI      nlaIII hhaI/cfoI                       nspBII bsh1236I                   dsaV fokI
         bsaAI tth111I/aspI bbvI                  aciI            aciI hgaI       drdI              cauII   aciI
5701 GCTATCGCTA CGTGACTGGG TCATGGCTGC GCCCCGACAC CCGCCAACAC CCGCTGACGC GCCCTGACGG GCTTGTCTGC TCCCGGCATC CGCTTACAGA
     CGATAGCGAT GCACTGACCC AGTACCGACG CGGGGCTGTG GGCGGTTGTG GGCGACTGCG CGGGACTGCC CGAACAGACG AGGGCCGTAG GCGAATGTCT
```

FIG. 48S

```
                                                                 thaI
                                                                 fnuDII/mvnI
                                                                 bstUI
                                                                 bsh1236I
              scrFI                                             hinPI
              nciI                                              hhaI/cfoI
              mspI                                             thaI mnlI                           mnlI
              hpaII      nspI                                  fnuDII/mvnI          mboII        haeIII/palI
              dsaV       nspHI                                 bstUI                bpuAI      sau96I
           esp3I       fnu4HI                                  bsh1236I             bbsI       asuI bssSI
           bsmBI       bsoFI                                                                  eco0109I/draII
       maeIII bsmAI    bbvI
    aluI     bslI  cauII aluI nlaIII     mnlI      hphI       hphI
5801 CAAGCTGTGA CCGTCTCCGG GAGCTGCATG TGTCAGAGGT TTTCACCGTC ATCACCGAAA CGCGCGAGGC AGTATTCTTG AAGACGAAAG GGCCTCGTGA
     GTTCGACACT GGCAGAGGCC CTCGACGTAC ACAGTCTCCA AAAGTGGCAG TAGTGGCTTT GCGCGCTCCG TCATAAGAAC TTCTGCTTTC CCGGAGCACT

                                                                                 nlaIV
                                                                               aciI
                                                                              thaI
                                                                              fnuDII/mvnI
                                                     hinlI/acyI               bstUI
                      nlaIII                         ahaII/bsaHI              bsh1236I
                 tru9I  rcaI                         aatII                   hinPI
                 mseI   bspHI                     ddeI maeII                 hhaI/cfoI
5901 TACGCCTATT TTTATAGGTT AATGTCATGA TAATAATGGT TTCTTAGACG TCAGGTGGCA CTTTTCGGGG AAATGTGCGC GGAACCCCTA TTTGTTTATT
     ATGCGGATAA AAATATCCAA TTACAGTACT ATTATTACCA AAGAATCTGC AGTCCACCGT GAAAAGCCCC TTTACACGCG CCTTGGGGAT AAACAAATAA

                            rcaI
                            bspHI                                                mboII
                          bsrBI   bsmAI                                 sspI     earI/ksp632I          mslI
                          aciI  nlaIII
6001 TTTCTAAATA CATTCAAATA TGTATCCGCT CATGAGACAA TAACCCTGAT AAATGCTTCA ATAATATTGA AAAAGGAAGA GTATGAGTAT TCAACATTTC
     AAAGATTTAT GTAAGTTTAT ACATAGGCGA GTACTCTGTT ATTGGGACTA TTTACGAAGT TATTATAACT TTTTCCTTCT CATACTCATA AGTTGTAAAG

                                                                                                  hgiAI/aspHI
                                                                                                  bsp1286
                                                                                        sau3AI    bsiHKAI
                                                                                        mboI/ndeII[dam-]
                                                                                        dpnI[dam+] bmyI
                                                                                        dpnII[dam-]
                          fnu4HI                                                   eco57I        apaLI/snoI
                          bsoFI                                              sfaNI  mboII[dam-]  alw44I/snoI
                          aciI                        hphI         hphI
6101 CGTGTCGCCC TTATTCCCTT TTTTGCGGCA TTTTGCCTTC CTGTTTTTGC TCACCCAGAA ACGCTGGTGA AAGTAAAAGA TGCTGAAGAT CAGTTGGGTG
     GCACAGCGGG AATAAGGGAA AAAACGCCGT AAAACGGAAG GACAAAAACG AGTGGGTCTT TGCGACCACT TTCATTTTCT ACGACTTCTA GTCAACCCAC
```

FIG. 48T

```
                    sau3AI    nspBII          sau3AI
                    mboI/ndeII[dam-]          mboI/ndeII[dam-]
                    dpnI[dam+]                dpnI[dam+]                  maeII
                   bstYI/xhoII                dpnII[dam-]                  psp1406I            hgiAI/aspHI
               bsrI dpnII[dam-]               alwI[dam-]                 xmnI                  bsp1286  tru9I
  bssSI    maeIII taqI  alwI[dam-]  aciI  bstYI/xhoII                    asp700                bsiHKAI  mseI
                                                                       mboII                   bmyI   ahaIII/draI
6201 CACGAGTGGG TTACATCGAA CTGGATCTCA ACAGCGGTAA GATCCTTGAG AGTTTTCGCC CCGAAGAACG TTTTCCAATG ATGAGCACTT TTAAAGTTCT
     GTGCTCACCC AATGTAGCTT GACCTAGAGT TGTCGCCATT CTAGGAACTC TCAAAAGCGG GGCTTCTTGC AAAAGGTTAC TACTCGTGAA AATTTCAAGA

                                 scrFI
           aciI                  nciI
          thaI                   mspI
          fnuDII/mvnI            hpaII
          bstUI                  dsaV                                                      rsaI
          bsh1236I             hinlI/acyI             aciI                                 csp6I   bsrI
         hinPI                 hgaI cauII         mcrI  fnu4HI                             scaI  hphI  maeIII
         hhaI/cfoI             ahaII/bsaHI    bcgI  bsiEI bsoFI      ddeI
6301 GCTATGTGGC GCGGTATTAT CCCGTGATGA CGCCGGGCAA GAGCAACTCG GTCGCCGCAT ACACTATTCT CAGAATGACT TGGTTGAGTA CTCACCAGTC
     CGATACACCG CGCCATAATA GGGCACTACT GCGGCCCGTT CTCGTTGAGC CAGCGGCGTA TGTGATAAGA GTCTTACTGA ACCAACTCAT GAGTGGTCAG

                                                                                                 sau3AI
                                                                          haeIII/palI            mboI/ndeII[dam-]
                                                                          eaeI                   dpnI[dam+]
                                                                          cfrI                   dpnII[dam-]
                                                  fnu4HI                  fnu4HI                pvuI/bspCI
                                                  bsoFI                   bsoFI                 mcrI
      sfaNI     fokI   nlaIII                     bbvI  mslI  nlaIII      aciI                  bsiEI
6401 ACAGAAAAGC ATCTTACGGA TGGCATGACA GTAAGAGAAT TATGCAGTGC TGCCATAACC ATGAGTGATA ACACTGCGGC CAACTTACTT CTGACAACGA
     TGTCTTTTCG TAGAATGCCT ACCGTACTGT CATTCTCTTA ATACGTCACG ACGGTATTGG TACTCACTAT TGTGACGCCG GTTGAATGAA GACTGTTGCT

                                                nlaIII
                                                sau3AI maeIII                        mspI
        sau96I                                  mboI/ndeII[dam-]       sau3AI   nlaIV
        avaII                                   dpnI[dam+]             mboI/ndeII[dam-] aluI
        asuI                                    dpnII[dam-]            dpnI[dam+]    hpaII
      mnlI        aluI    aciI            nlaIII alwI[dam-]            dpnII[dam-] bsaWI
6501 TCGGAGGACC GAAGGAGCTA ACCGCTTTTT TGCACAACAT GGGGGATCAT GTAACTCGCC TTGATCGTTG GGAACCGGAG CTGAATGAAG CCATACCAAA
     AGCCTCCTGG CTTCCTCGAT TGGCGAAAAA ACGTGTTGTA CCCCCTAGTA CATTGAGCGG AACTAGCAAC CCTTGGCCTC GACTTACTTC GGTATGGTTT
```

FIG. 48U

```
                                                   hinPI                                                          mspI
                                                   hhaI/cfoI                                                      hpaII
                           fnu4HI                  mstI                                                  aluI     scrFI
                           bsoFI                   aviII/fspI      bsrI                                 rmaI      nciI        tru9I
             mslI      cac8I  bsrDI            maeII              tru9I                                  maeI      dsaV        mseI
         maeIII     sfaNI  bbvI               psp1406I             mseI                                  bfaI      cauII       aseI/asnI/vspI
6601 CGACGAGCGT GACACCACGA TGCCAGCAGC AATGGCAACA ACGTTGCGCA AACTATTAAC TGGCGAACTA CTTACTCTAG CTTCCCGGCA ACAATTAATA
     GCTGCTCGCA CTGTGGTGCT ACGGTCGTCG TTACCGTTGT TGCAACGCGT TTGATAATTG ACCGCTTGAT GAATGAGATC GAAGGGCCGT TGTTAATTAT

                                                   bglI                                                            mspI
                                                   sau96I      cac8I                                               hpaII
                                  sau96I           haeIII/palI                                                     cfr10I/bsrFI
      fokI      aciI              avaII        hinPI  asuI      mspI                                         nlaIV hphI      bsmAI
     bsrI    mnlI                 asuI         hhaI/cfoI        hpaII                                      bpmI/gsuI[dcm-]   bsaI
6701 GACTGGATGG AGGCGGATAA AGTTGCAGGA CCACTTCTGC GCTCGGCCCT TCCGGCTGGC TGGTTTATTG CTGATAAATC TGGAGCCGGT GAGCGTGGGT
     CTGACCTACC TCCGCCTATT TCAACGTCCT GGTGAAGACG CGAGCCGGGA AGGCCGACCG ACCAAATAAC GACTATTTAG ACCTCGGCCA CTCGCACCCA

       aciI
      thaI          fnu4HI     haeIII/palI                                                   pleI
      fnuDII/mvnI   bsoFI       sau96I                                                       hinfI
      bstUI         bbvI       nlaIV                                                    ahdI/eam1105I        fokI
      bsh1236I bsrDI     bsrI asuI              mnlI
6801 CTCGCGGTAT CATTGCAGCA CTGGGGCCAG ATGGTAAGCC CTCCCGTATC GTAGTTATCT ACACGACGGG GAGTCAGGCA ACTATGGATG AACGAAATAG
     GAGCGCCATA GTAACGTCGT GACCCCGGTC TACCATTCGG GAGGGCATAG CATCAATAGA TGTGCTGCCC CTCAGTCCGT TGATACCTAC TTGCTTTATC

          ddeI
       sau3AI        nlaIV                                                                             tru9I
       mboI/ndeII[dam-]                                                                                mseI          tru9I
       dpnI[dam+]    hgiCI        tru9I                                                             ahaIII/draI      mseI
       dpnII[dam-]   banI mnlI    mseI       maeIII
6901 ACAGATCGCT GAGATAGGTG CCTCACTGAT TAAGCATTGG TAACTGTCAG ACCAAGTTTA CTCATATATA CTTTAGATTG ATTTAAAACT TCATTTTTAA
     TGTCTAGCGA CTCTATCCAC GGAGTGACTA ATTCGTAACC ATTGACAGTC TGGTTCAAAT GAGTATATAT GAAATCTAAC TAAATTTTGA AGTAAAAATT

             rmaI
             maeI      sau3AI
          sau3AI hphI  mboI/ndeII[dam-]
          mboI/ndeII[dam-]
          dpnI[dam+]   dpnI[dam+]                                                                                       sau3AI
          dpnII[dam-]  dpnII[dam-]                                    maeII                                             mboI/ndeII[dam-]
      tru9I bstYI/xhoII  alwI[dam-]              nlaIII              tru9I                        hgaI                   dpnI[dam+]
      mseI  alwI[dam-]  bstYI/xhoII               rcaI                mseI                    ddeI                       dpnII[dam-]
     ahaIII/draI bfaI  mboII[dam-]               bspHI
7001 TTTAAAAGGA TCTAGGTGAA GATCCTTTTT GATAATCTCA TGACCAAAAT CCCTTAACGT GAGTTTTCGT TCCACTGAGC GTCAGACCCC GTAGAAAAGA
     AAATTTTCCT AGATCCACTT CTAGGAAAAA CTATTAGAGT ACTGGTTTTA GGGAATTGCA CTCAAAAGCA AGGTGACTCG CAGTCTGGGG CATCTTTTCT
```

FIG. 48V

```
                      sau3AI
          mboII[dam-]
        sau3AI        mboI/ndeII[dam-]  thaI
        mboI/ndeII[dam-]                fnuDII/mvnI
        dpnI[dam+]    dpnI[dam+]        bstUI           cac8I
        dpnII[dam-]   dpnII[dam-]       bsh1236I    fnu4HI
       bstYI/xhoII    alwI[dam-]       hinPI       bsoFI
       alwI[dam-]    bstYI/xhoII       hhaI/cfoI   bbvI
7101 TCAAAGGATC TTCTTGAGAT CCTTTTTTTC TGCGCGTAAT CTGCTGCTTG CAAACAAAAA
     AGTTTCCTAG AAGAACTCTA GGAAAAAAAG ACGCGCATTA GACGACGAAC GTTTGTTTTT

                                   sau3AI
                                   mboI/ndeII[dam-]
                                   dpnI[dam+]
                                   dpnII[dam-]
                                  alwI[dam-]
                  aciI           mspI
        aciI    nspBII           hpaII        aluI
     AACCACCGCT ACCAGCGGTG GTTTGTTTGC CGGATCAAGA
     TTGGTGGCGA TGGTCGCCAC CAAACAAACG GCCTAGTTCT

                                                        rmaI
                                         hinPI          maeI                haeIII/palI
                       bsrI                             bfaI      bslI     haeI
                     maeIII     eco57I   hhaI/cfoI
7201 GCTACCAACT CTTTTTCCGA AGGTAACTGG CTTCAGCAGA GCGCAGATAC CAAATACTGT CCTTCTAGTG TAGCCGTAGT TAGGCCACCA CTTCAAGAAC
     CGATGGTTGA GAAAAAGGCT TCCATTGACC GAAGTCGTCT CGCGTCTATG GTTTATGACA GGAAGATCAC ATCGGCATCA ATCCGGTGGT GAAGTTCTTG

                                                  fnu4HI
                                                  bsoFI
                                                  bbvI
                                              fnu4HI                         scrFI
                                          alwNI[dcm-]                        nciI
                                         bsrI  bsoFI                         mspI
                                               bbvI      bsrI                hpaII
                                                                             dsaV     pleI
                                    maeIII                                   cauII    hinfI
      scfI    aciI       mnlI
7301 TCTGTAGCAC CGCCTACATA CCTCGCTCTG CTAATCCTGT TACCAGTGGC TGCTGCCAGT GGCGATAAGT CGTGTCTTAC CGGGTTGGAC TCAAGACGAT
     'AGACATCGTG GCGGATGTAT GGAGCGAGAC GATTAGGACA ATGGTCACCG ACGACGGTCA CCGCTATTCA GCACAGAATG GCCCAACCTG AGTTCTGCTA

                  aciI
                 nspBII                      hgiAI/aspHI
                fnu4HI                       bsp1286
       mspI     bsoFI                        bsiHKAI
        hpaII   bbvI  mcrI                   bmyI
       bsaWI   hinPI  bsiEI                  apaLI/snoI
     maeIII    hhaI/cfoI                     alw44I/snoI  aluI                     ddeI       scfI
7401 AGTTACCGGA TAAGGCGCAG CGGTCGGGCT GAACGGGGGG TTCGTGCACA CAGCCCAGCT TGGAGCGAAC GACCTACACC GAACTGAGAT ACCTACAGCG
     TCAATGGCCT ATTCCGCGTC GCCAGCCCGA CTTGCCCCCC AAGCACGTGT GTCGGGTCGA ACCTCGCTTG CTGGATGTGG CTTGACTCTA TGGATGTCGC
```

FIG. 48W

```
                                                                                                          scrFI
                                                                                                          mvaI
                                                                                                          ecoRII
                                                                                                          dsaV
                                                          mspI                             bssSI          bstNI
           hinPI                                          hpaII  fnu4HI                  hinPI mnlI       bsaJI
           hhaI/cfoI                                      bslI   bsoFI                   hhaI/cfoI  aluI apyI[dcm+]
          haeII                               aciI       bsaWI   aciI
7501 TGAGCATTGA GAAAGCGCCA CGCTTCCCGA AGGGAGAAAG GCGGACAGGT ATCCGGTAAG CGGCAGGGTC GGAACAGGAG AGCGCACGAG GGAGCTTCCA
     ACTCGTAACT CTTTCGCGGT GCGAAGGGCT TCCCTCTTTC CGCCTGTCCA TAGGCCATTC GCCGTCCCAG CCTTGTCCTC TCGCGTGCTC CCTCGAAGGT

          scrFI
          mvaI
          ecoRII
          dsaV                                                                                       nlaIV
          bstNI                                                            taqI                    aciI
          apyI[dcm+]                                   mnlI drdI        hgaI            sfaNI
7601 GGGGGAAACG CCTGGTATCT TTATAGTCCT GTCGGGTTTC GCCACCTCTG ACTTGAGCGT CGATTTTTGT GATGCTCGTC AGGGGGGCGG AGCCTATGGA
     CCCCCTTTGC GGACCATAGA AATATCAGGA CAGCCCAAAG CGGTGGAGAC TGAACTCGCA GCTAAAAACA CTACGAGCAG TCCCCCCGCC TCGGATACCT

             haeIII/palI           haeIII/palI
            fnu4HI               scrFI
            bsoFI                mvaI bslI
            aciI                 ecoRII
           thaI bslI             dsaV                        nlaIII
           fnuDII/mvnI           bstNI              haeIII/palI  nspI
           bstUI                 apyI[dcm+]        haeI         nspHI                      tfiI
     cac8I bsh1236I        nlaIV  haeI            cac8I         aflIII                     hinfI
7701 AAAACGCCAG CAACGCGGCC TTTTTACGGT TCCTGGCCTT TTGCTGGCCT TTTGCTCACA TGTTCTTTCC TGCGTTATCC CCTGATTCTG TGGATAACCG
     TTTTGCGGTC GTTGCGCCGG AAAAATGCCA AGGACCGGAA AACGACCGGA AAACGAGTGT ACAAGAAAGG ACGCAATAGG GGACTAAGAC ACCTATTGGC

                                   fnu4HI
                                   bsoFI                 fnu4HI
                                   bbvI                  bsoFI                        sapI  hinPI
                              cac8I aciI                 bbvI pleI                     mboII hhaI/cfoI
                             bsrBI  fnu4HI        mcrI   hinPI  hinfI                  earI/ksp632I
        aciI           aluI  aciI   bsoFI         bsiEI  hhaI/cfoI            mnlI  aciI   haeII
7801 TATTACCGCC TTTGAGTGAG CTGATACCGC TCGCCGCAGC CGAACGACCG AGCGCAGCGA GTCAGTGAGC GAGGAAGCGG AAGAGCGCCC AATACGCAAA
     ATAATGGCGG AAACTCACTC GACTATGGCG AGCGGCGTCG GCTTGCTGGC TCGCGTCGCT CAGTCACTCG CTCCTTCGCC TTCTCGCGGG TTATGCGTTT
```

FIG. 48X

```
                   thaI
                   fnuDII/mvnI
                   bstUI
                   bsh1236I
                  hinPI
                  hhaI/cfoI
                 thaI                                  cac8I
                 fnuDII/mvnI                          aluI
                 bstUI   haeIII/palI                 pvuII                                                                tru9I
                 bsh1236I           tru9I                                            cac8I         hinPI             mseI        maeIII
      mnlI       bslI      eaeI   tfiI aseI/asnI/vspI                        bsrI        aciI          hhaI/cfoI  aseI/asnI/vspI
     aciI        aciI      cfrI   hinfI mseI    nspBII
7901 CCGCCTCTCC CCGCGCGTTG GCCGATTCAT TAATCCAGCT GGCACGACAG GTTTCCCGAC TGGAAAGCGG GCAGTGAGCG CAACGCAATT AATGTGAGTT
     GGCGGAGAGG GGCGCGCAAC CGGCTAAGTA ATTAGGTCGA CCGTGCTGTC CAAAGGGCTG ACCTTTCGCC CGTCACTCGC GTTGCGTTAA TTACACTCAA

                      scrFI
                      mvaI
                      ecoRII
                      dsaV
                 nlaIV bstNI                                                aciI
                 hgiCI apyI[dcm+]                mspI                      bsrBI                             aluI
      mnlI       banI bsaJI                      hpaII
8001 ACCTCACTCA TTAGGCACCC CAGGCTTTAC ACTTTATGCT TCCGGCTCGT ATGTTGTGTG GAATTGTGAG CGGATAACAA TTTCACACAG GAAACAGCTA
     TGGAGTGAGT AATCCGTGGG GTCCGAAATG TGAAATACGA AGGCCGAGCA TACAACACAC CTTAACACTC GCCTATTGTT AAAGTGTGTC CTTTGTCGAT
```

FIG. 48Y

```
                     tru9I
                     mseI
                    aseI/asnI/vspI
                   xmnI
         nlaIII    asp700
  8101 TGACCATGAT TACGAATTAA   (SEQ ID NO.68)
       ACTGGTACTA ATGCTTAATT

>length: 8120

aatII(GACGTC):          1690 5947
acc65I(GGTACC):         2969 3967 4529
accI(GTMKAC):           823 1039 2738 4237
aciI(CCGC):             217 229 238 250 260 271 317 422 454 485 574 1385 1795 1871 2248 2250 2758 2982
                        3167 3179 3188 3200 3210 3221 3267 3372 3404 3449 3686 3949 4021 4318 4542 4727
                        4739 4748 4760 4770 4781 4827 4910 4914 5070 5127 5153 5166 5203 5217 5220 5248
                        5275 5680 5699 5741 5751 5790 5979 6026 6125 6234 6311 6355 6476 6522 6713 6804
                        7166 7175 7310 7420 7541 7560 7687 7715 7806 7827 7834 7877 7901 7911 7967 8070
acyI                    see hinlI
aflII/bfrI(CTTAAG):     786
aflIII(ACRYGT):         932 7758
ageI(ACCGGT):           1833
ahaII/bsaHI(GRCGYC):    988 1690 1858 5117 5947 6329
ahaIII/draI(TTTAAA):    696 4935 6290 6982 7001
ahdI/eam1105I(GACNNNNNGTC): 2087 6865
aluI(AGCT):             5 44 332 386 390 753 1097 1165 1370 1431 1951 2603 2751 2784 3282 3336 3340
                        3562 3566 3676 3733 3792 4270 4288 4311 4344 4554 4842 4896 4954 5047 5333 5590
                        5803 5822 6516 6579 6679 7200 7457 7593 7819 7937 8096
alw44I/snoI(GTGCAC):    1876 5651 6198 7444
```

FIG. 48Z

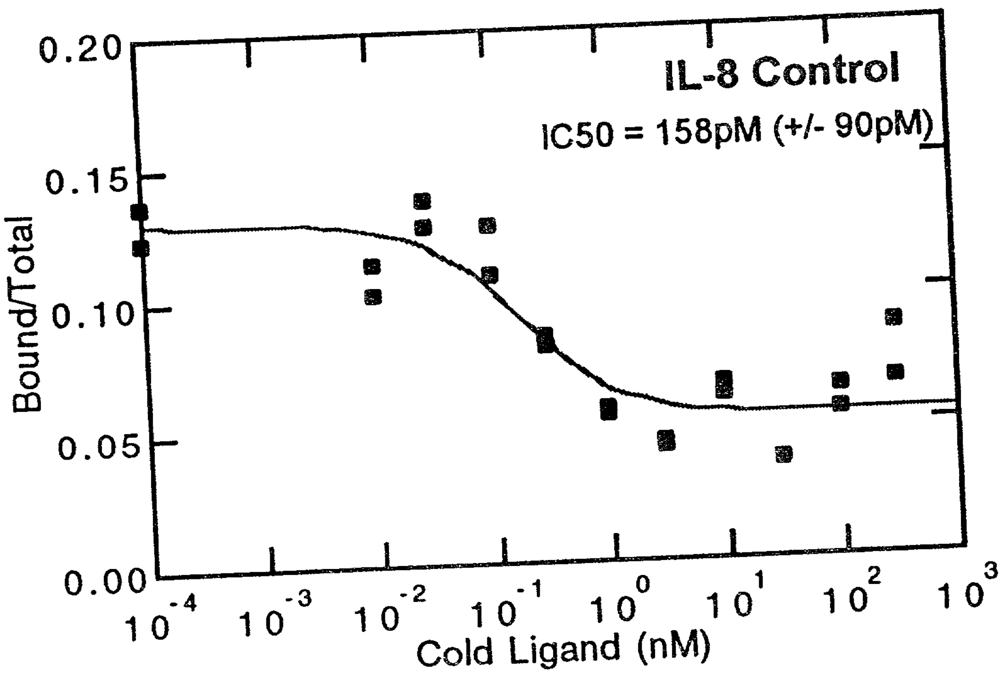


FIG. 49A

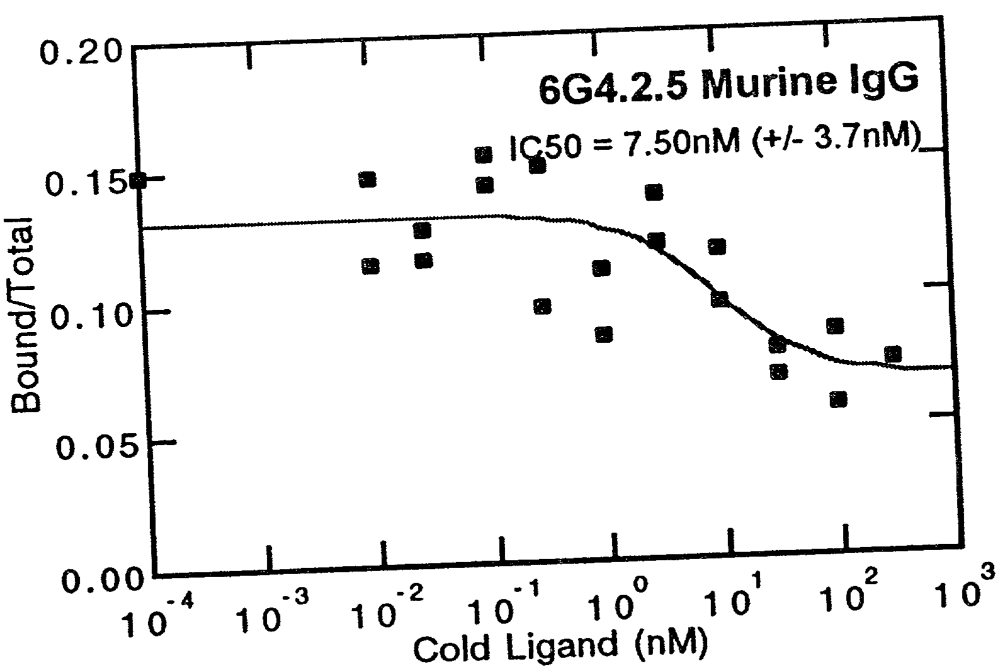


FIG. 49B

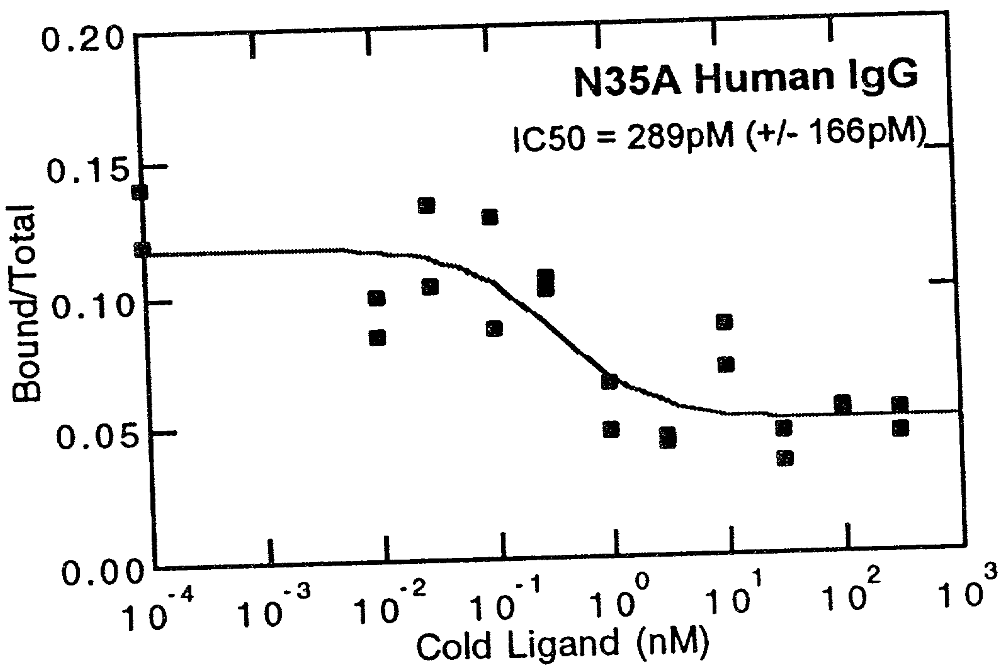


FIG. 49C

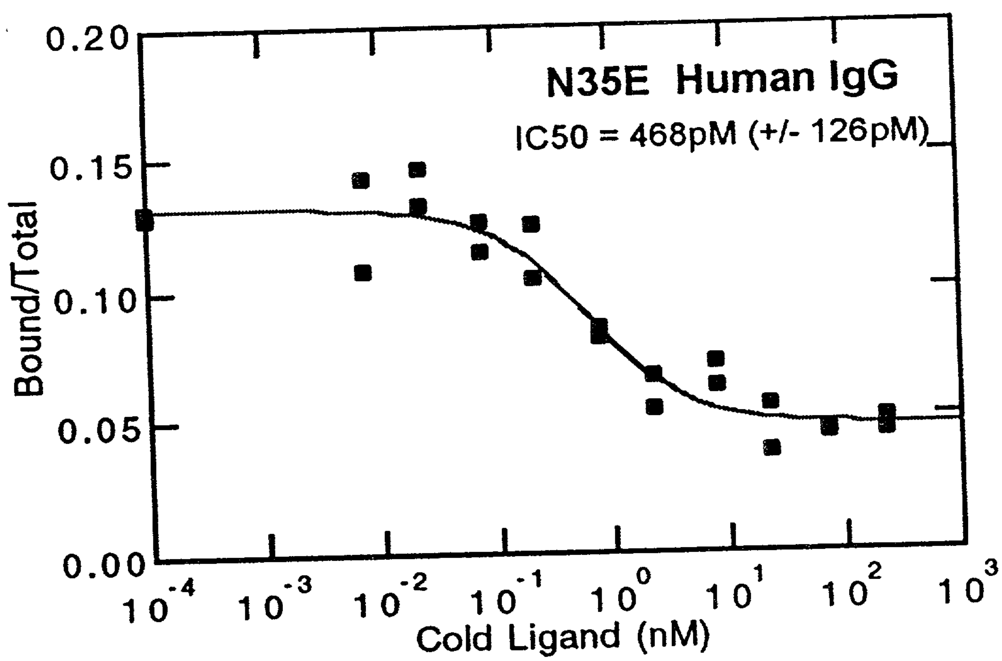


FIG. 49D

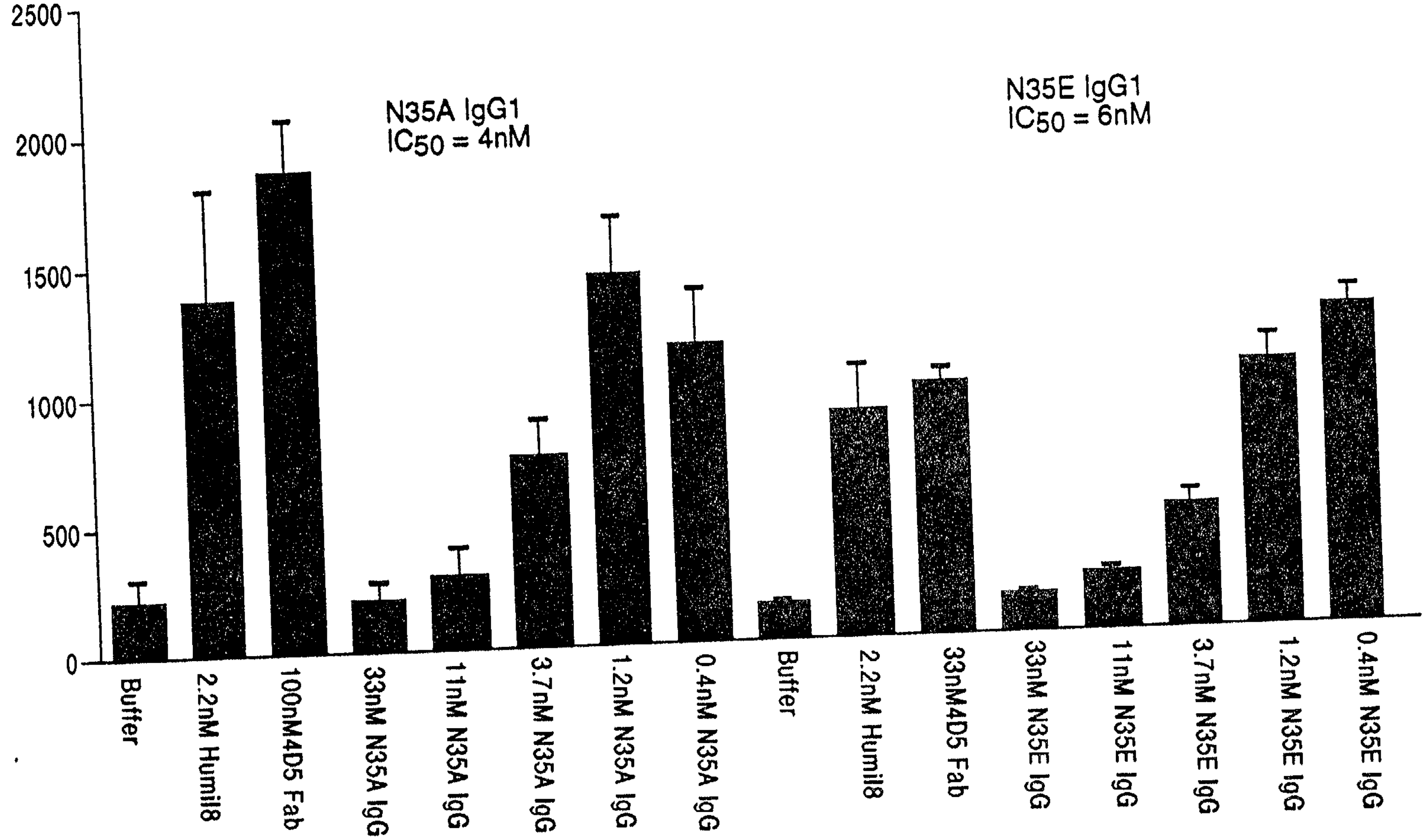

2500
2000
1500
1000
500
0
N35A IgG1
IC_{50} = 4nM
N35E IgG1
IC_{50} = 6nM
Buffer
2.2nM Humil8
100nM4D5 Fab
33nM N35A IgG
11nM N35A IgG
3.7nM N35A IgG
1.2nM N35A IgG
0.4nM N35A IgG
Buffer
2.2nM Humil8
33nM4D5 Fab
33nM N35E IgG
11nM N35E IgG
3.7nM N35E IgG
1.2nM N35E IgG
0.4nM N35E IgG

FIG. 50A

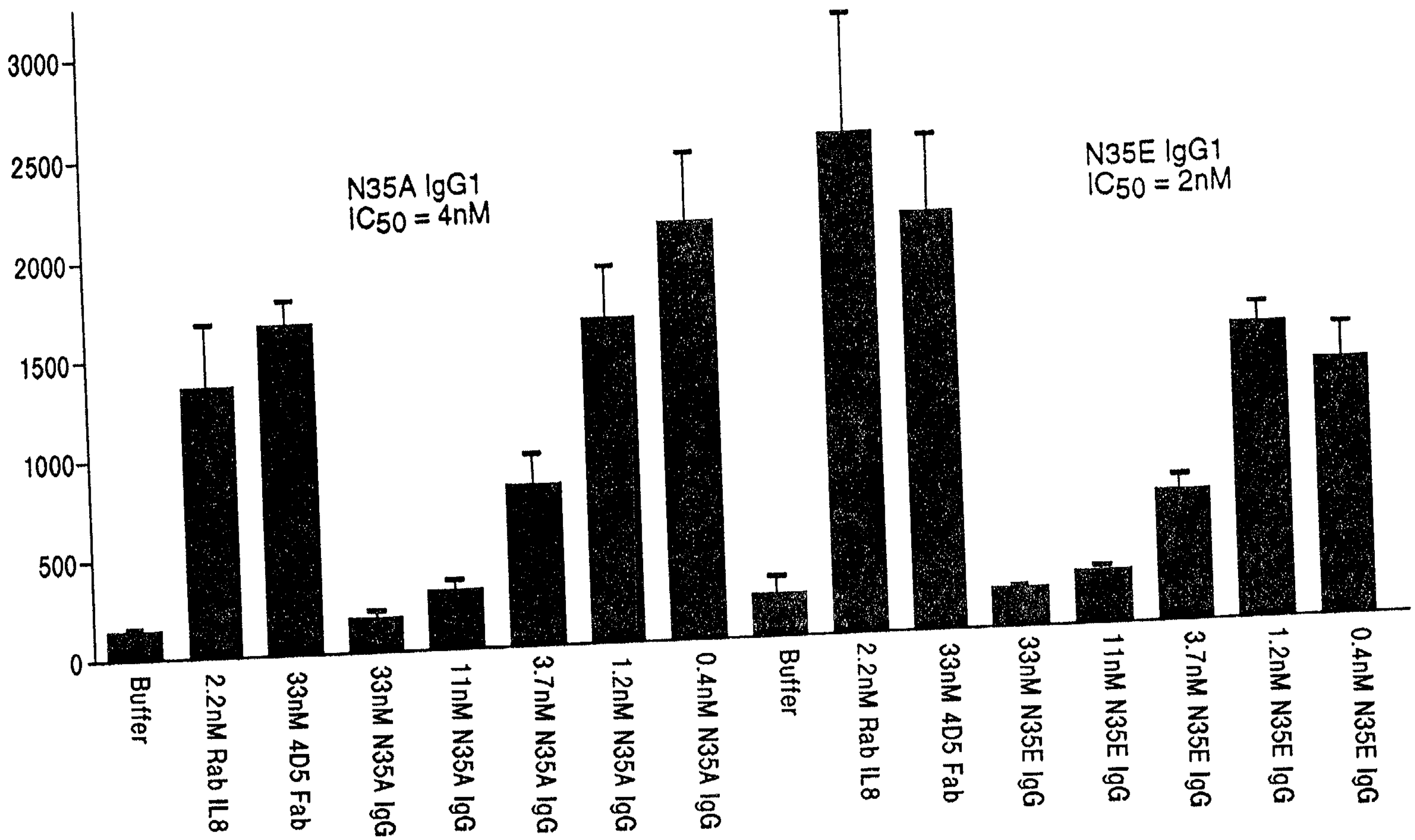
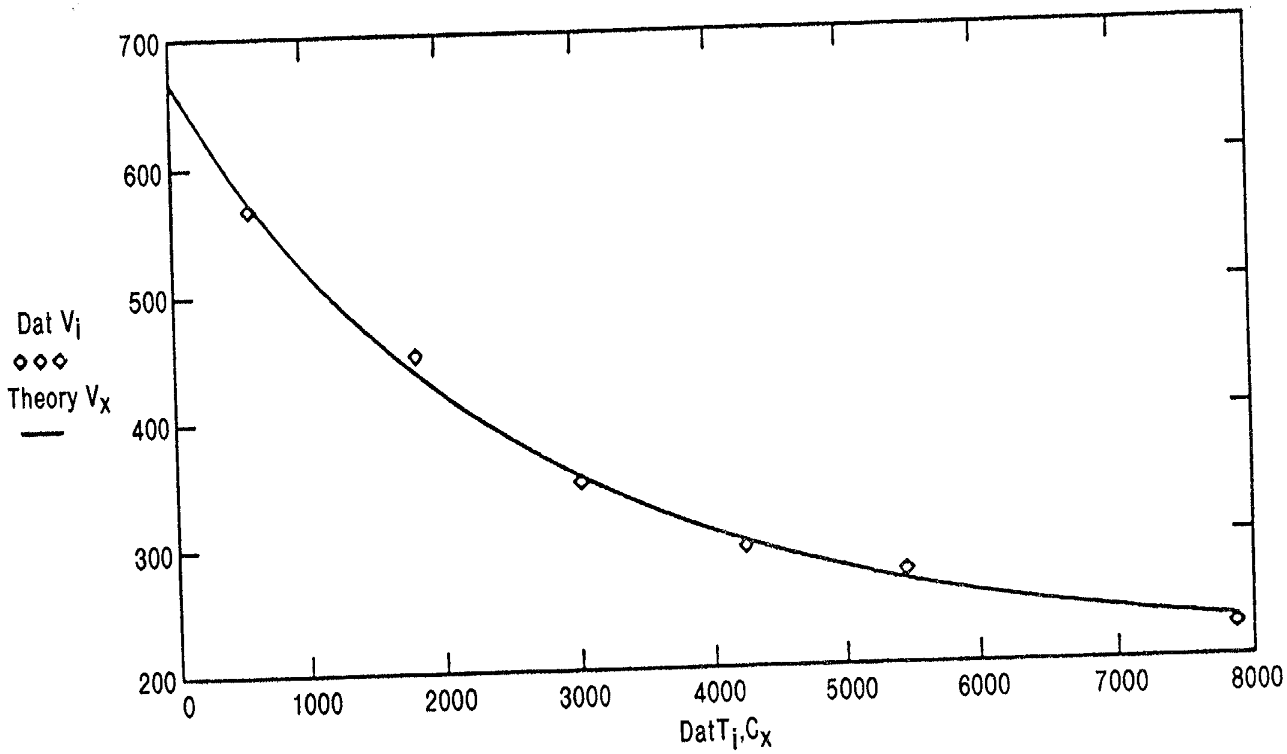

3000
2500
2000
1500
1000
500
0
N35A IgG1
IC50 = 4nM
N35E IgG1
IC50 = 2nM
Buffer
2.2nM Rab IL8
33nM 4D5 Fab
33nM N35A IgG
11nM N35A IgG
3.7nM N35A IgG
1.2nM N35A IgG
0.4nM N35A IgG
Buffer
2.2nM Rab IL8
33nM 4D5 Fab
33nM N35E IgG
11nM N35E IgG
3.7nM N35E IgG
1.2nM N35E IgG
0.4nM N35E IgG

FIG. 50B



Representative Conc versus Time Plot. Shown is the kinetic data for 6G4V11N35A.IgG1

SAMPLE	ka	kd	Kd
Murine 6G4.2.5 IgG2a	8.3×10^5	2.9×10^{-4}	350pM
6G4V11N35A-IgG1	8.7×10^5	7.7×10^{-5}	88pM
6G4V11N35E-IgG1	3.0×10^6	1.4×10^{-4}	49pM

FIG. 51

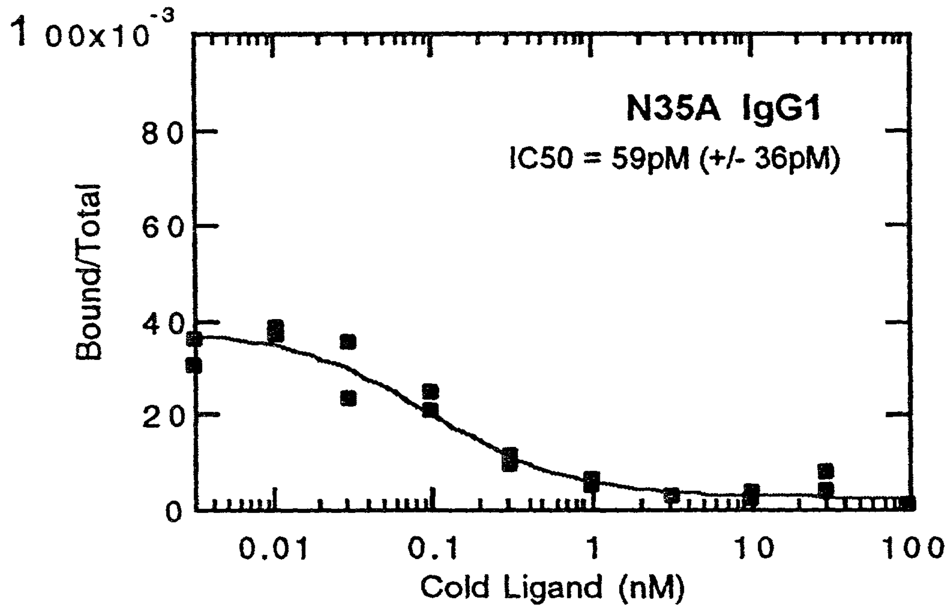


FIG. 52A

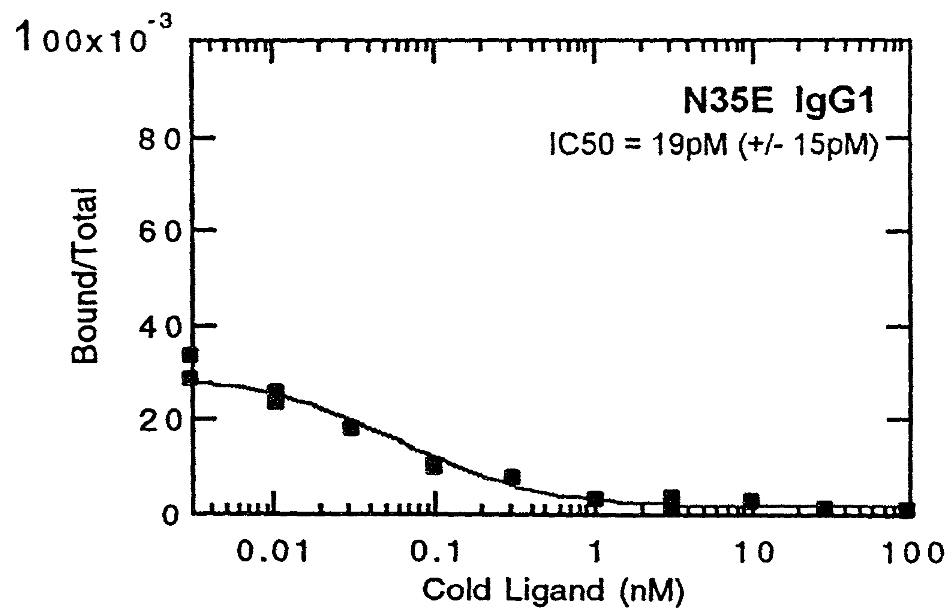


FIG. 52B

```
781  AAAAGGGTAT CTAGAGGTTG AGGTGATTTT ATGAAAAAGA ATATCGCATT TCTTCTTGCA
     TTTTCCCATA GATCTCCAAC TCCACTAAAA TACTTTTTCT TATAGCGTAA AGAAGAACGT
-1                                    M  K  K  N   I  A  F   L  L  A

841  TCTATGTTCG TTTTTTCTAT TGCTACAAAC GCGTACGCTG AGGTTCAGCT AGTGCAGTCT
     AGATACAAGC AAAAAAGATA ACGATGTTTG CGCATGCGAC TCCAAGTCGA TCACGTCAGA
-11  S  M  F  V   F  S  I   A  T  N   A  Y  A  E   V  Q  L   V  Q  S

901  GGCGGTGGCC TGGTGCAGCC AGGGGGCTCA CTCCGTTTGT CCTGTGCAGC TTCTGGCTAC
     CCGCCACCGG ACCACGTCGG TCCCCCGAGT GAGGCAAACA GGACACGTCG AAGACCGATG
8    G  G  G  L   V  Q  P   G  G  S   L  R  L  S   C  A  A   S  G  Y

961  TCCTTCTCGA GTCACTATAT GCACTGGGTC CGTCAGGCCC CGGGTAAGGG CCTGGAATGG
     AGGAAGAGCT CAGTGATATA CGTGACCCAG GCAGTCCGGG GCCCATTCCC GGACCTTACC
28   S  F  S  S   H  Y  M   H  W  V   R  Q  A  P   G  K  G   L  E  W

1021 GTTGGATATA TTGATCCTTC CAATGGTGAA ACTACGTATA ATCAAAAGTT CAAGGGCCGT
     CAACCTATAT AACTAGGAAG GTTACCACTT TGATGCATAT TAGTTTTCAA GTTCCCGGCA
48   V  G  Y  I   D  P  S   N  G  E   T  T  Y  N   Q  K  F   K  G  R

1081 TTCACTTTAT CTCGCGACAA CTCCAAAAAC ACAGCATACC TGCAGATGAA CAGCCTGCGT
     AAGTGAAATA GAGCGCTGTT GAGGTTTTTG TGTCGTATGG ACGTCTACTT GTCGGACGCA
68   F  T  L  S   R  D  N   S  K  N   T  A  Y  L   Q  M  N   S  L  R

1141 GCTGAGGACA CTGCCGTCTA TTACTGTGCA AGAGGGGATT ATCGCTACAA TGGTGACTGG
     CGACTCCTGT GACGGCAGAT AATGACACGT TCTCCCCTAA TAGCGATGTT ACCACTGACC
88   A  E  D  T   A  V  Y   Y  C  A   R  G  D  Y   R  Y  N   G  D  W

1201 TTCTTCGACG TCTGGGGTCA AGGAACCCTG GTCACCGTCT CCTCGGCCTC CACCAAGGGC
     AAGAAGCTGC AGACCCCAGT TCCTTGGGAC CAGTGGCAGA GGAGCCGGAG GTGGTTCCCG
108  F  F  D  V   W  G  Q   G  T  L   V  T  V  S   S  A  S   T  K  G

1261 CCATCGGTCT TCCCCCTGGC ACCCTCCTCC AAGAGCACCT CTGGGGGCAC AGCGGCCCTG
     GGTAGCCAGA AGGGGGACCG TGGGAGGAGG TTCTCGTGGA GACCCCCGTG TCGCCGGGAC
128  P  S  V  F   P  L  A   P  S  S   K  S  T  S   G  G  T   A  A  L

1321 GGCTGCCTGG TCAAGGACTA CTTCCCCGAA CCGGTGACGG TGTCGTGGAA CTCAGGCGCC
     CCGACGGACC AGTTCCTGAT GAAGGGGCTT GGCCACTGCC ACAGCACCTT GAGTCCGCGG
148  G  C  L  V   K  D  Y   F  P  E   P  V  T  V   S  W  N   S  G  A

1381 CTGACCAGCG GCGTGCACAC CTTCCCGGCT GTCCTACAGT CCTCAGGACT CTACTCCCTC
     GACTGGTCGC CGCACGTGTG GAAGGGCCGA CAGGATGTCA GGAGTCCTGA GATGAGGGAG
168  L  T  S  G   V  H  T   F  P  A   V  L  Q  S   S  G  L   Y  S  L

1441 AGCAGCGTGG TGACCGTGCC CTCCAGCAGC TTGGGCACCC AGACCTACAT CTGCAACGTG
     TCGTCGCACC ACTGGCACGG GAGGTCGTCG AACCCGTGGG TCTGGATGTA GACGTTGCAC
188  S  S  V  V   T  V  P   S  S  S   L  G  T  Q   T  Y  I   C  N  V

1501 AATCACAAGC CCAGCAACAC CAAGGTCGAC AAGAAAGTTG AGCCCAAATC TTGTGACAAA
     TTAGTGTTCG GGTCGTTGTG GTTCCAGCTG TTCTTTCAAC TCGGGTTTAG AACACTGTTT
208  N  H  K  P   S  N  T   K  V  D   K  K  V  E   P  K  S   C  D  K

1561 ACTCACACAT GCCCGCCGTGA  (SEQ ID NO.69)
     TGAGTGTGTA CGGGCGGCACT
228  T  H  T  C   P  P  O    (SEQ ID NO.70)
```

FIG. 53

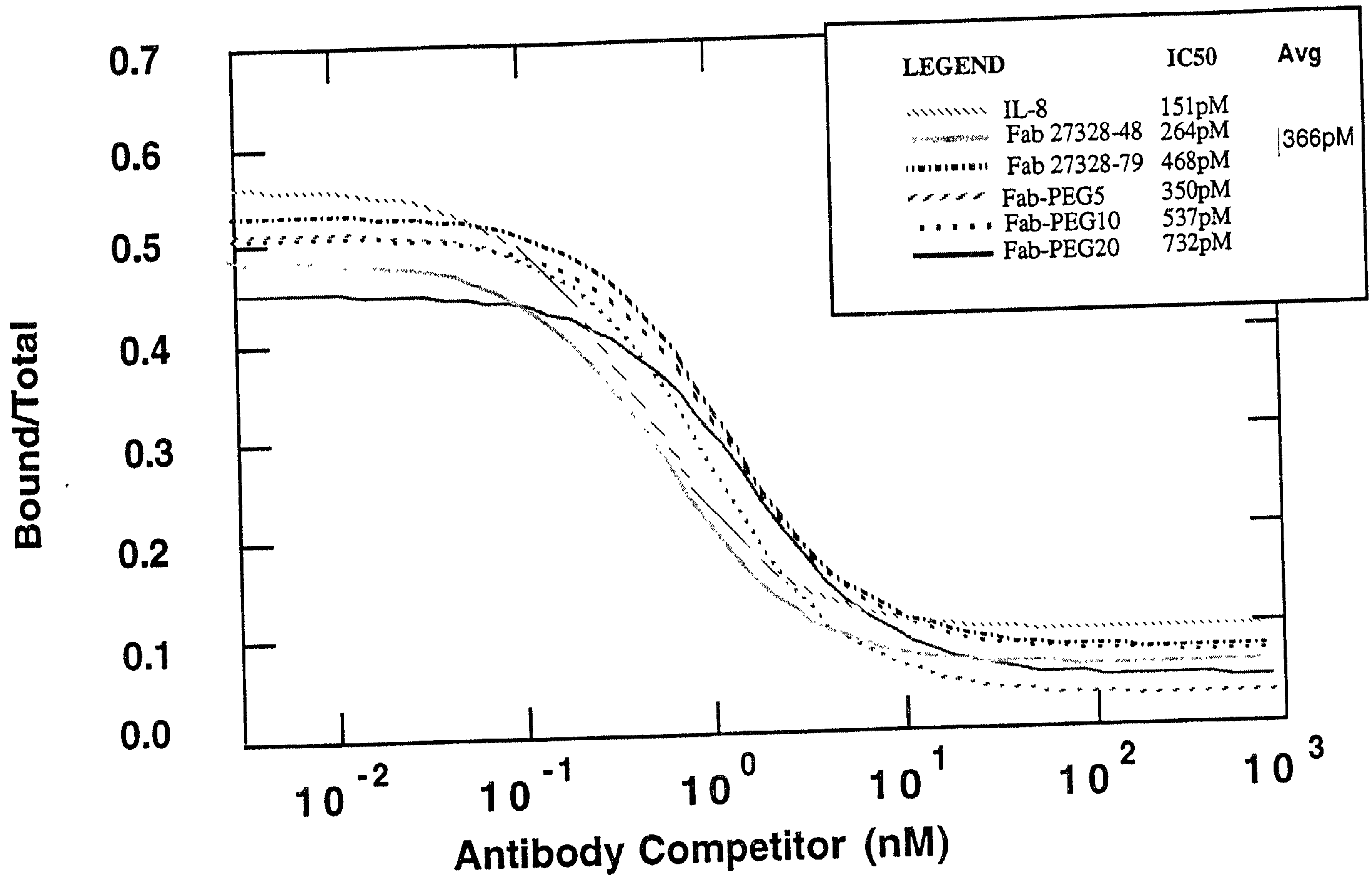

0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Bound/Total
LEGEND
IC50
Avg
IL-8 151pM
Fab 27328-48 264pM
Fab 27328-79 468pM
Fab-PEG5 350pM
Fab-PEG10 537pM
Fab-PEG20 732pM
366pM
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
10^{3}
Antibody Competitor (nM)

FIG. 54A

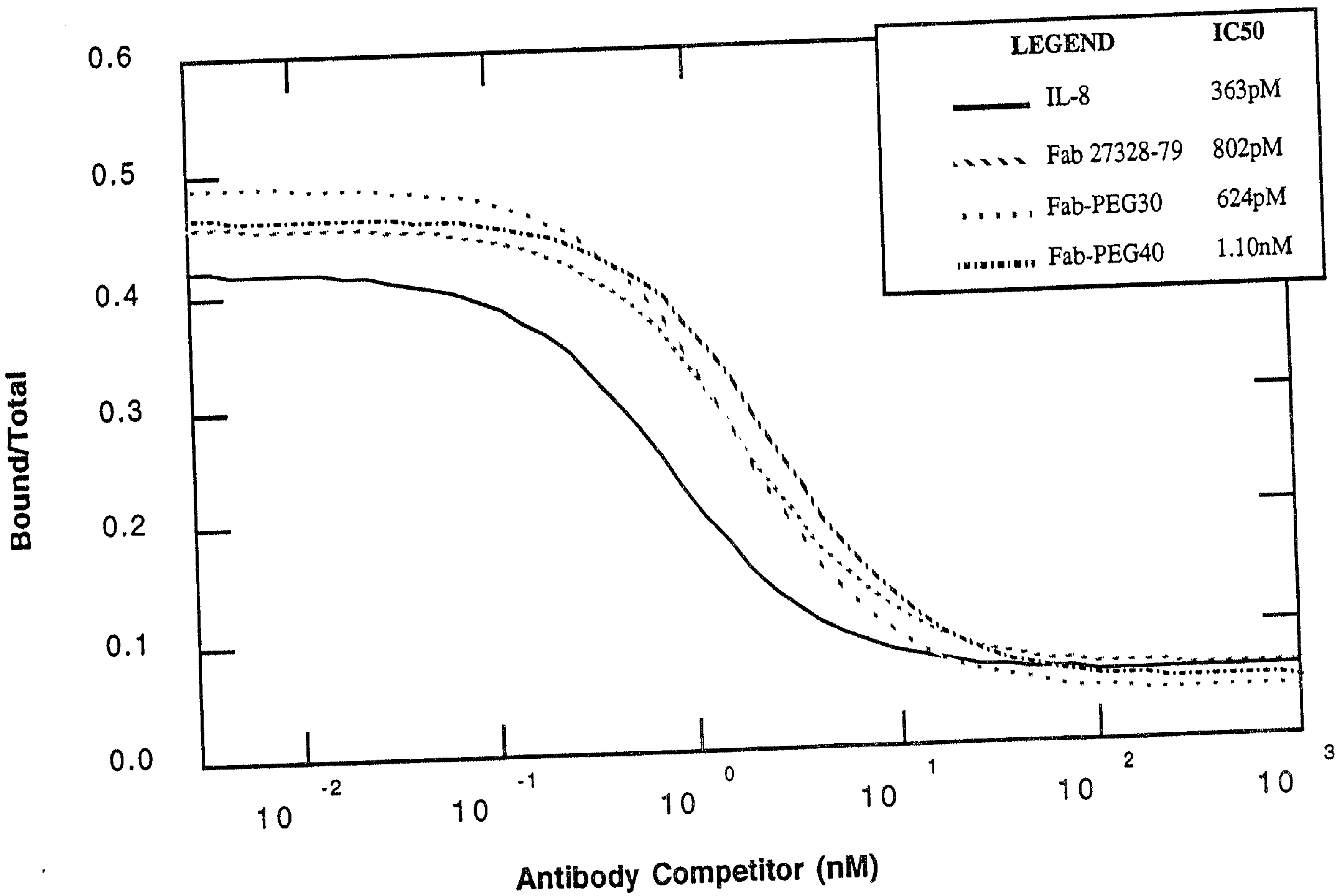
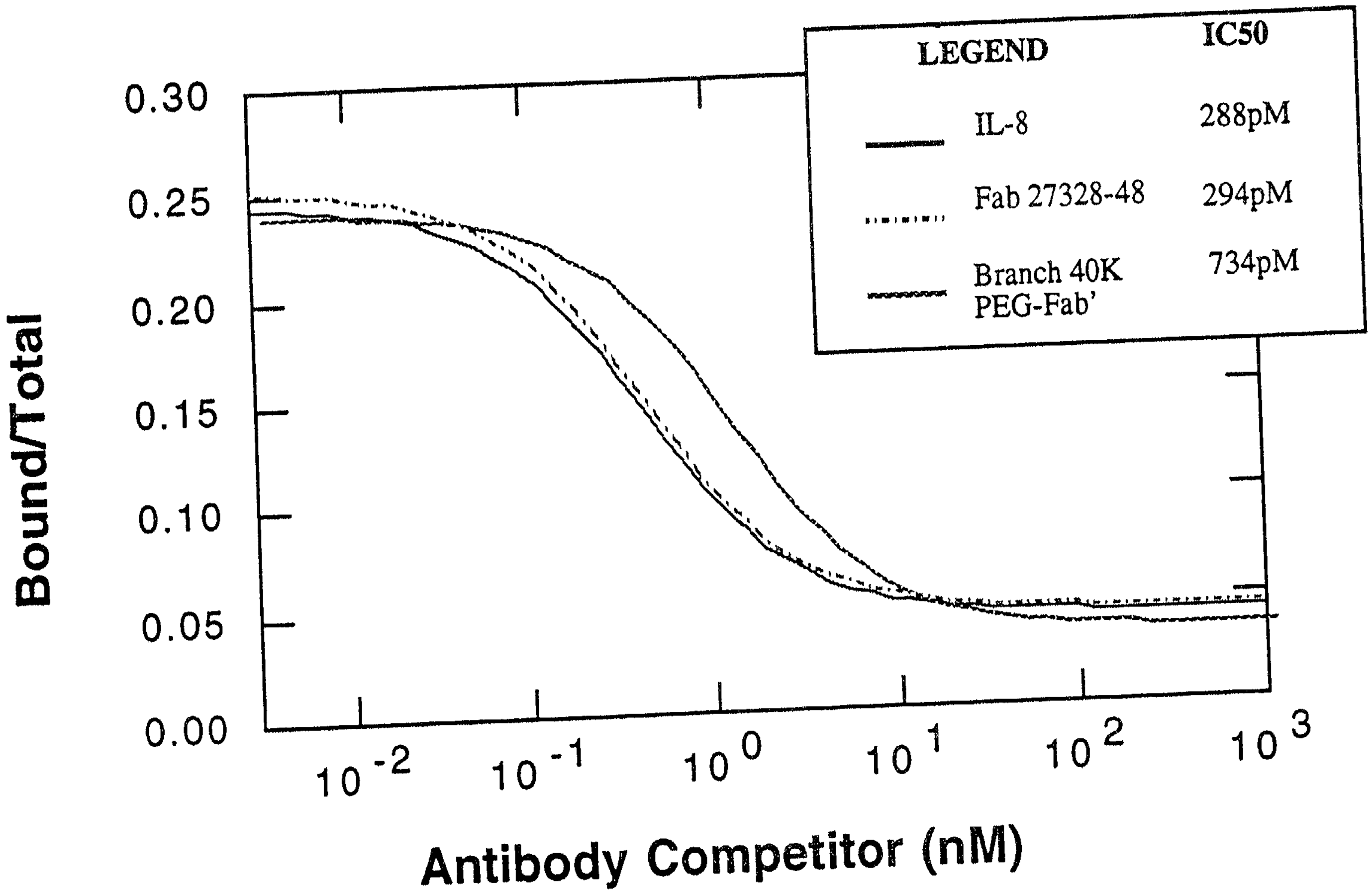

LEGEND
IC50
IL-8
363pM
Fab 27328-79
802pM
Fab-PEG30
624pM
Fab-PEG40
1.10nM
Bound/Total
0.6
0.5
0.4
0.3
0.2
0.1
0.0
10^-2
10^-1
10^0
10^1
10^2
10^3
Antibody Competitor (nM)

FIG. 54B



LEGEND
IC50
IL-8
288pM
Fab 27328-48
294pM
Branch 40K PEG-Fab'
734pM
0.30
0.25
0.20
0.15
0.10
0.05
0.00
Bound/Total
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
10^{3}
Antibody Competitor (nM)

FIG. 54C

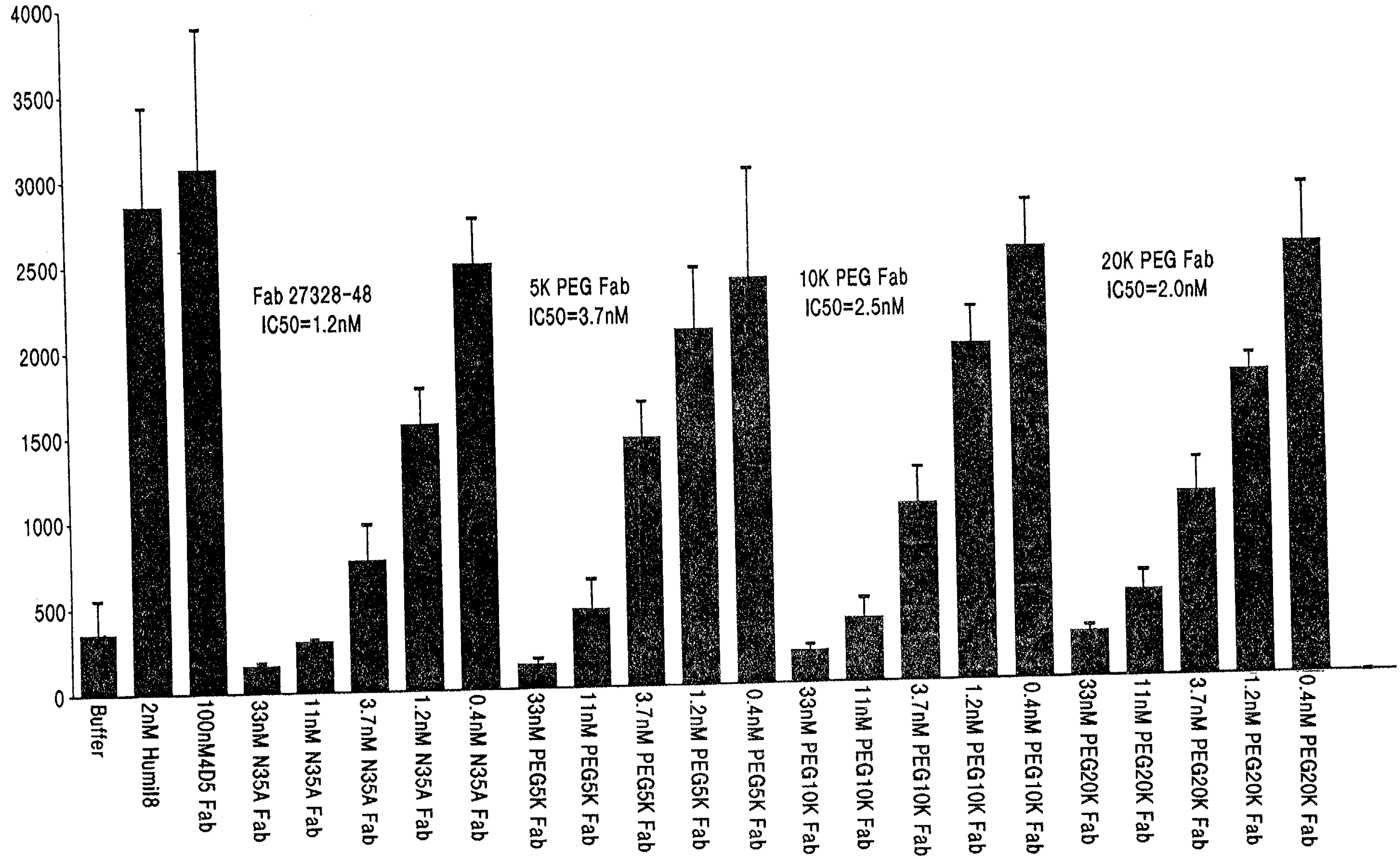

4000
3500
3000
2500
2000
1500
1000
500
0
Fab 27328-48
IC50=1.2nM
5K PEG Fab
IC50=3.7nM
10K PEG Fab
IC50=2.5nM
20K PEG Fab
IC50=2.0nM
Buffer
2nM Humil8
100nM4D5 Fab
33nM N35A Fab
11nM N35A Fab
3.7nM N35A Fab
1.2nM N35A Fab
0.4nM N35A Fab
33nM PEG5K Fab
11nM PEG5K Fab
3.7nM PEG5K Fab
1.2nM PEG5K Fab
0.4nM PEG5K Fab
33nM PEG10K Fab
11nM PEG10K Fab
3.7nM PEG10K Fab
1.2nM PEG10K Fab
0.4nM PEG10K Fab
33nM PEG20K Fab
11nM PEG20K Fab
3.7nM PEG20K Fab
1.2nM PEG20K Fab
0.4nM PEG20K Fab

FIG. 55A

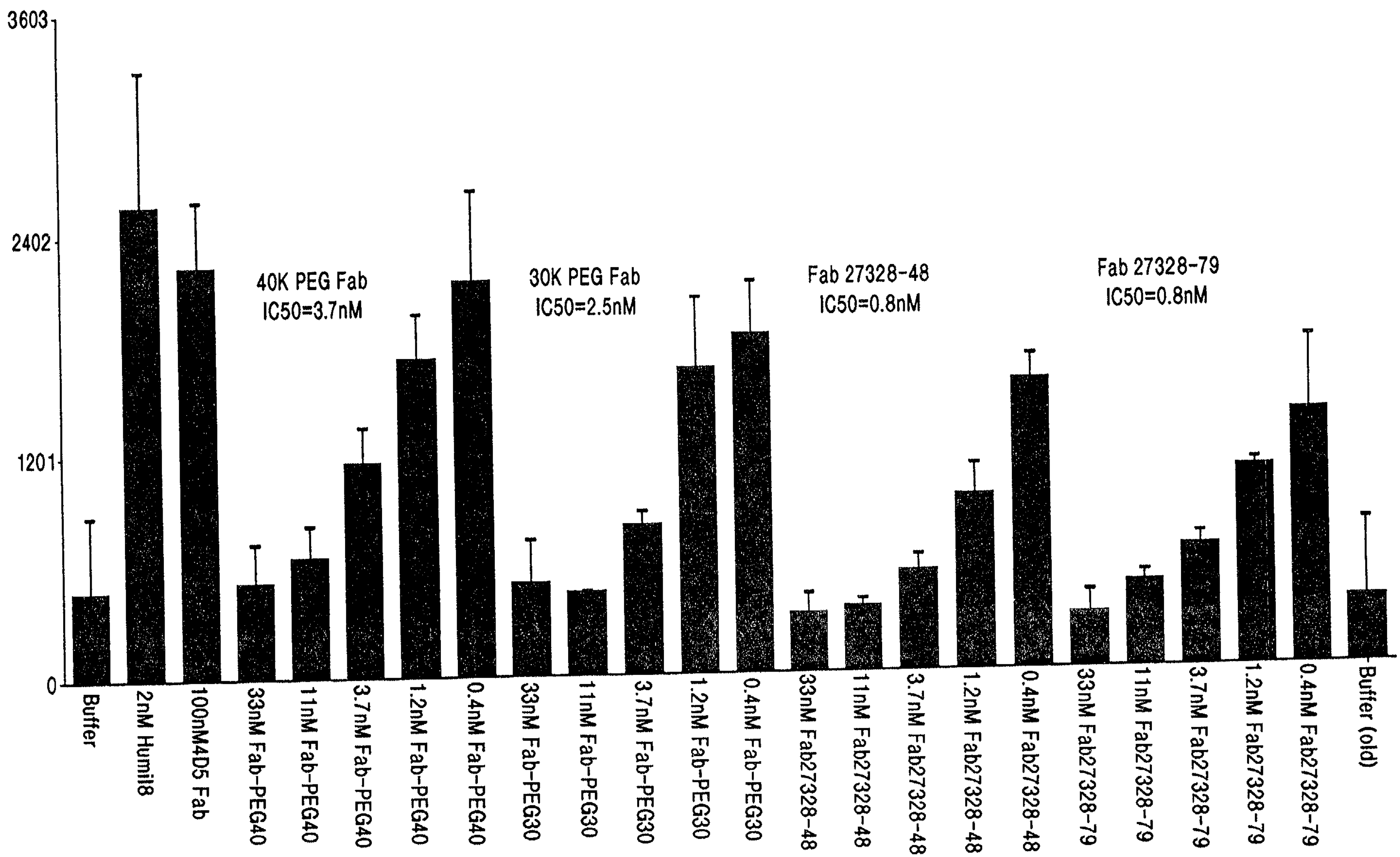
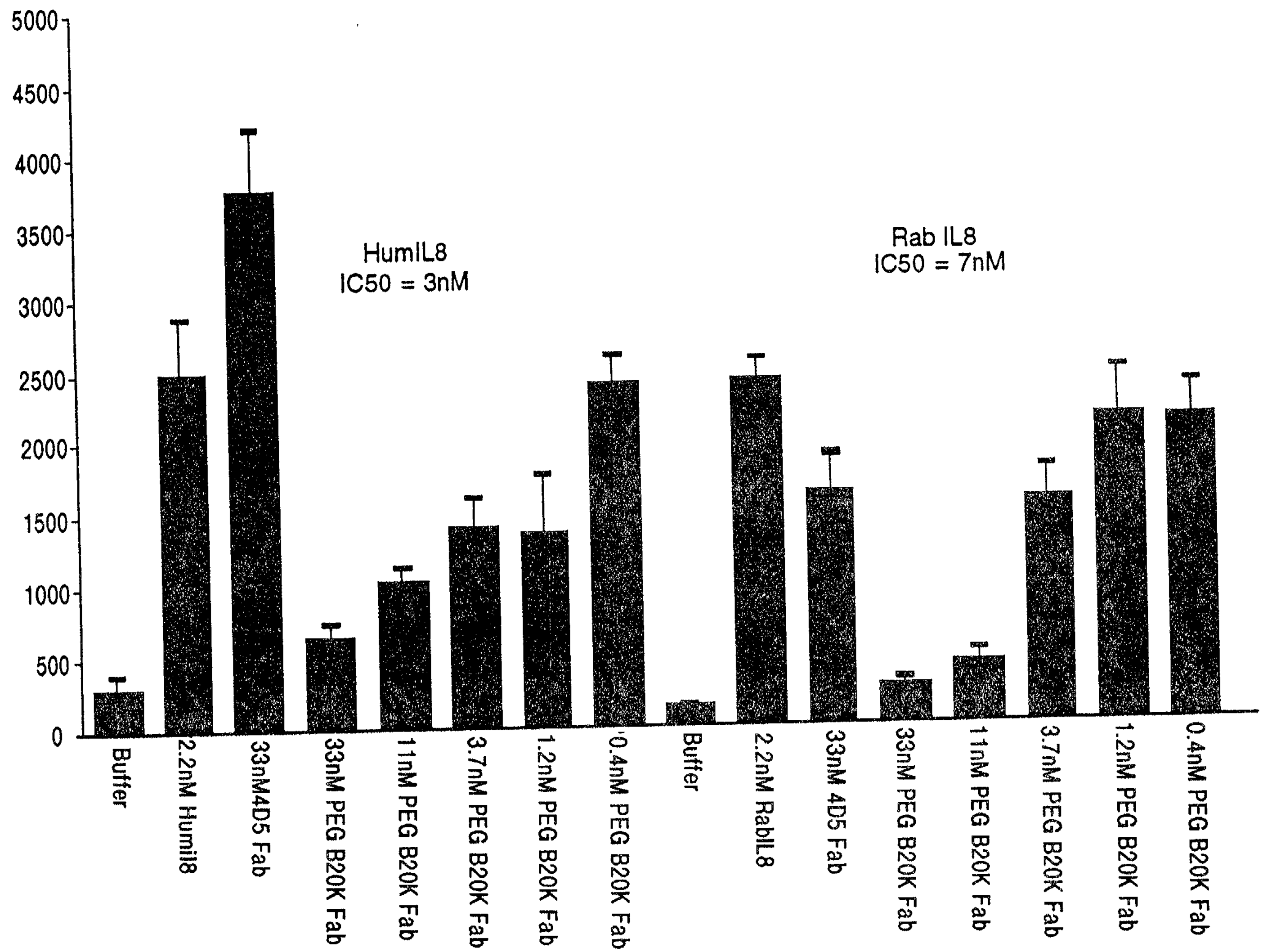

3603
2402
1201
0
40K PEG Fab
IC50=3.7nM
30K PEG Fab
IC50=2.5nM
Fab 27328-48
IC50=0.8nM
Fab 27328-79
IC50=0.8nM
Buffer
2nM Humil8
100nM4D5 Fab
33nM Fab-PEG40
11nM Fab-PEG40
3.7nM Fab-PEG40
1.2nM Fab-PEG40
0.4nM Fab-PEG40
33nM Fab-PEG30
11nM Fab-PEG30
3.7nM Fab-PEG30
1.2nM Fab-PEG30
0.4nM Fab-PEG30
33nM Fab27328-48
11nM Fab27328-48
3.7nM Fab27328-48
1.2nM Fab27328-48
0.4nM Fab27328-48
33nM Fab27328-79
11nM Fab27328-79
3.7nM Fab27328-79
1.2nM Fab27328-79
0.4nM Fab27328-79
Buffer (old)

FIG. 55B



5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
HumIL8
IC50 = 3nM
Rab IL8
IC50 = 7nM
Buffer
2.2nM Humil8
33nM4D5 Fab
33nM PEG B20K Fab
11nM PEG B20K Fab
3.7nM PEG B20K Fab
1.2nM PEG B20K Fab
0.4nM PEG B20K Fab
Buffer
2.2nM RabIL8
33nM 4D5 Fab
33nM PEG B20K Fab
11nM PEG B20K Fab
3.7nM PEG B20K Fab
1.2nM PEG B20K Fab
0.4nM PEG B20K Fab

FIG. 55C

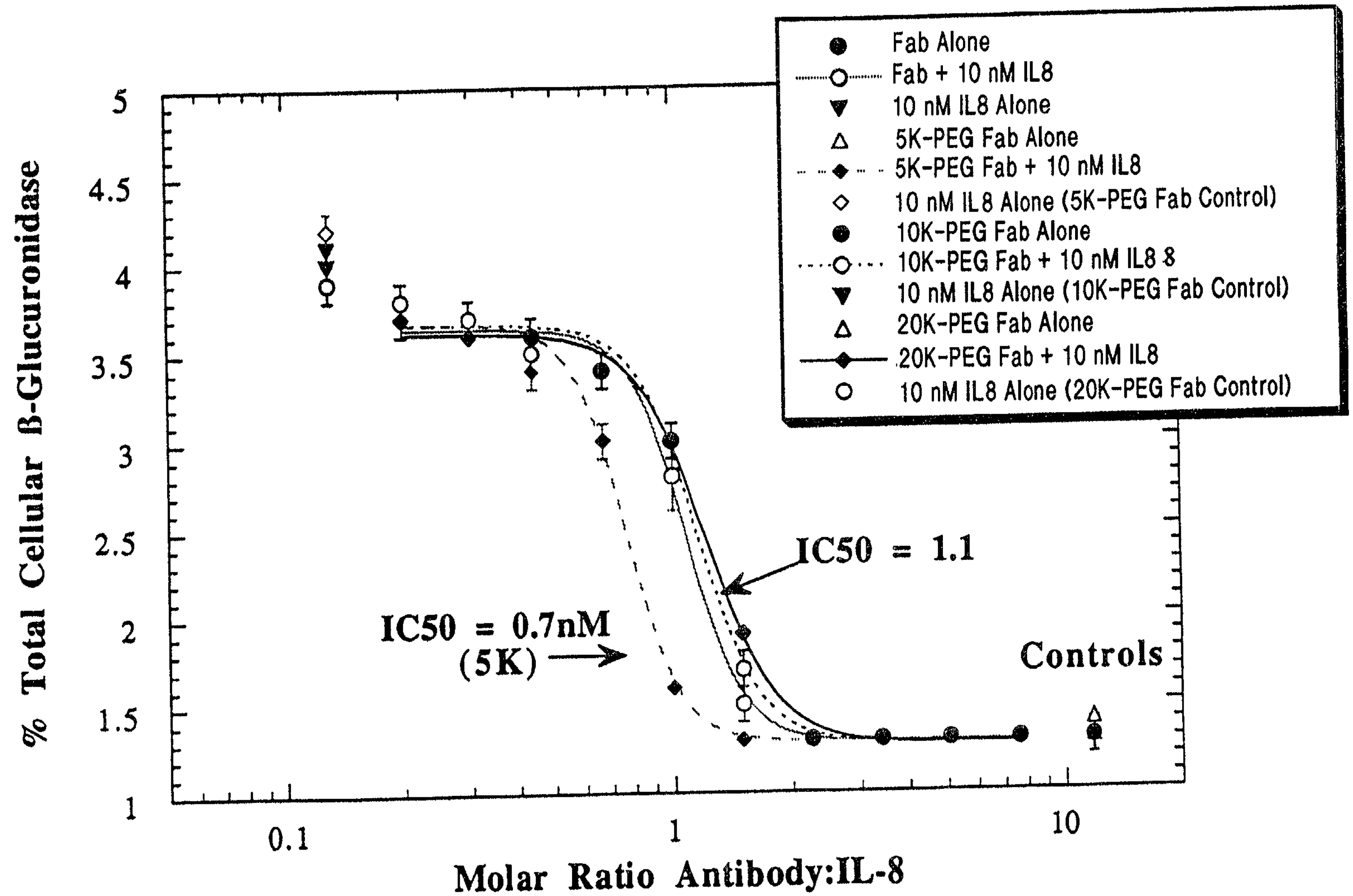

% Total Cellular ß-Glucuronidase
5
4.5
4
3.5
3
2.5
2
1.5
1
0.1
1
10
Molar Ratio Antibody:IL-8
IC50 = 1.1
IC50 = 0.7nM
(5K)
Controls
Fab Alone
Fab + 10 nM IL8
10 nM IL8 Alone
5K-PEG Fab Alone
5K-PEG Fab + 10 nM IL8
10 nM IL8 Alone (5K-PEG Fab Control)
10K-PEG Fab Alone
10K-PEG Fab + 10 nM IL8 8
10 nM IL8 Alone (10K-PEG Fab Control)
20K-PEG Fab Alone
20K-PEG Fab + 10 nM IL8
10 nM IL8 Alone (20K-PEG Fab Control)

FIG. 56A

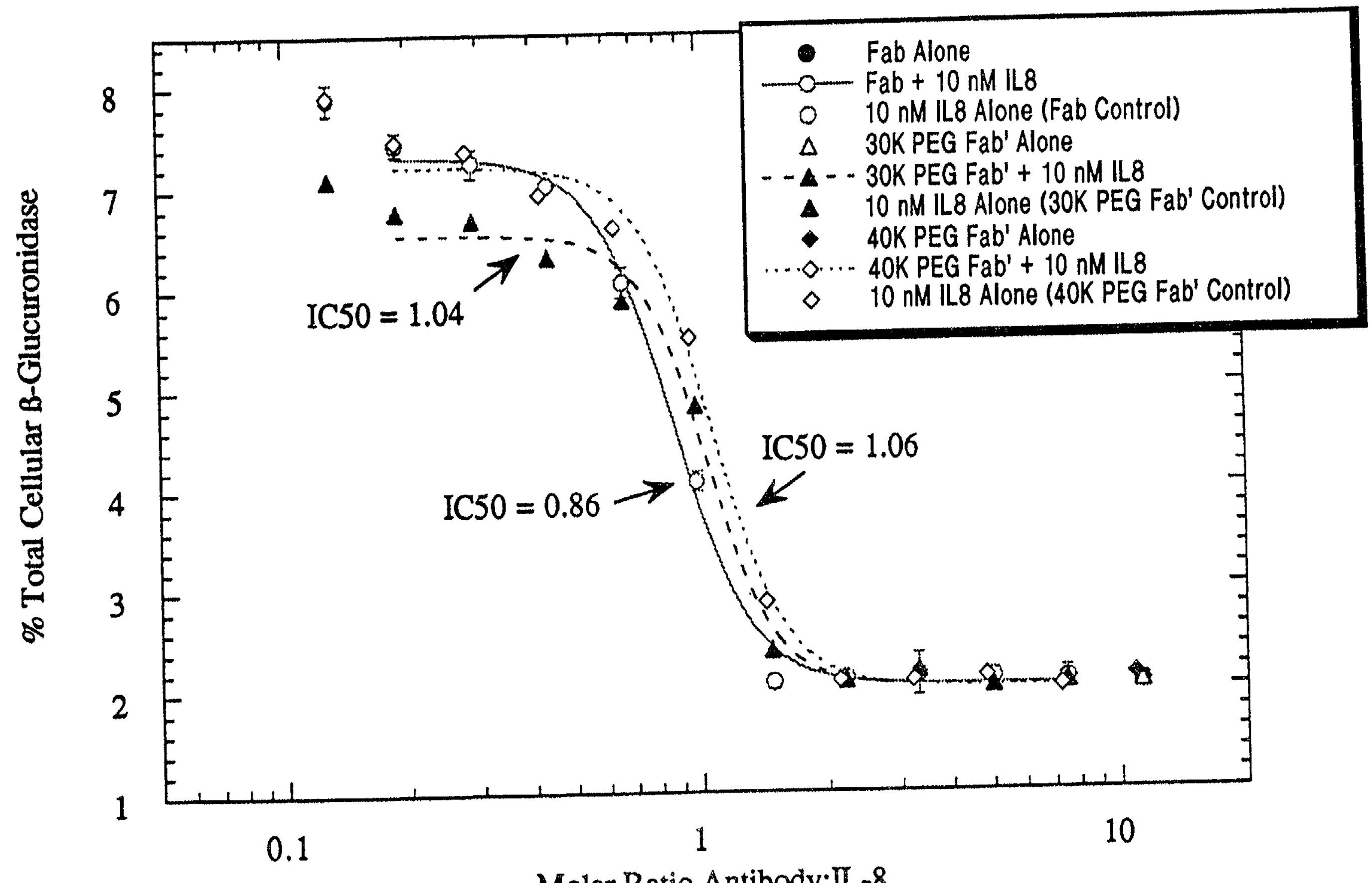

Fab Alone
Fab + 10 nM IL8
10 nM IL8 Alone (Fab Control)
30K PEG Fab' Alone
30K PEG Fab' + 10 nM IL8
10 nM IL8 Alone (30K PEG Fab' Control)
40K PEG Fab' Alone
40K PEG Fab' + 10 nM IL8
10 nM IL8 Alone (40K PEG Fab' Control)
IC50 = 1.04
IC50 = 0.86
IC50 = 1.06
% Total Cellular ß-Glucuronidase
Molar Ratio Antibody:IL-8
0.1
1
10
1
2
3
4
5
6
7
8

FIG. 56B

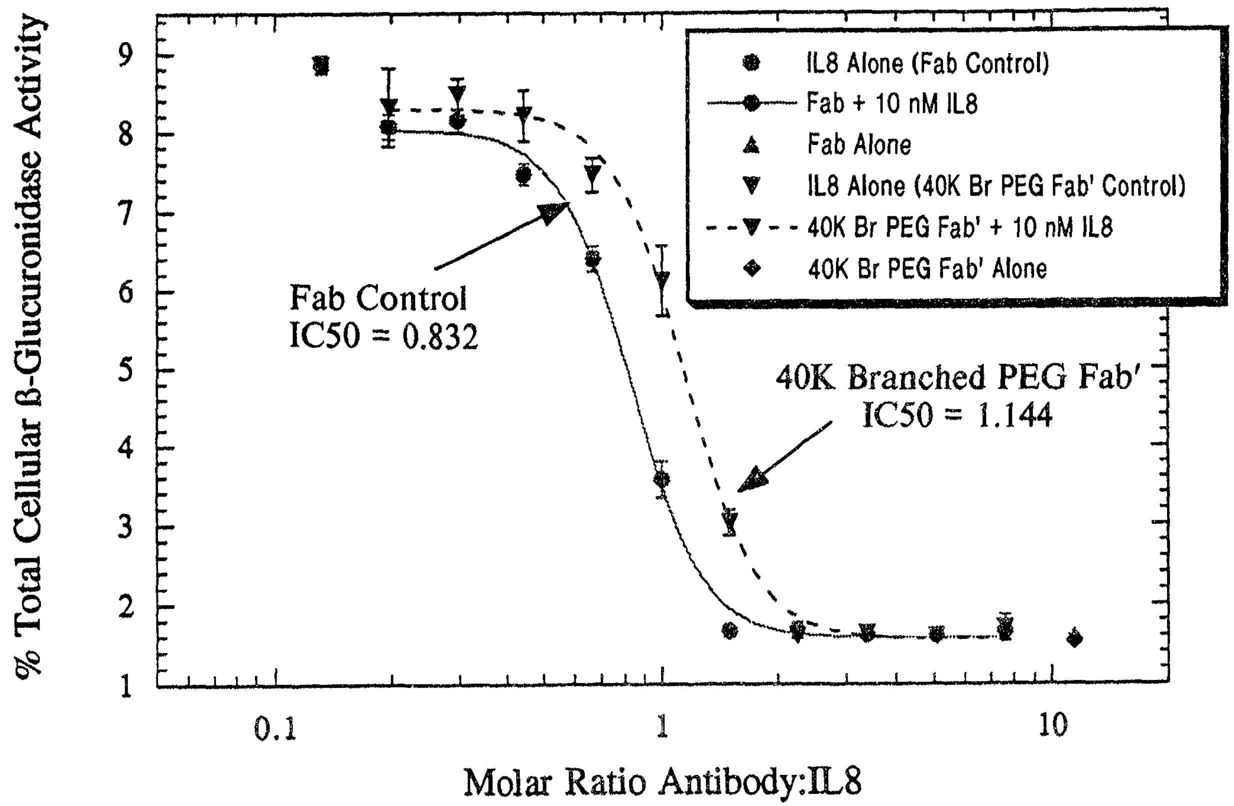

% Total Cellular β-Glucuronidase Activity
9
8
7
6
5
4
3
2
1
0.1
1
10
Molar Ratio Antibody:IL8
IL8 Alone (Fab Control)
Fab + 10 nM IL8
Fab Alone
IL8 Alone (40K Br PEG Fab' Control)
40K Br PEG Fab' + 10 nM IL8
40K Br PEG Fab' Alone
Fab Control
IC50 = 0.832
40K Branched PEG Fab'
IC50 = 1.144

FIG. 56C

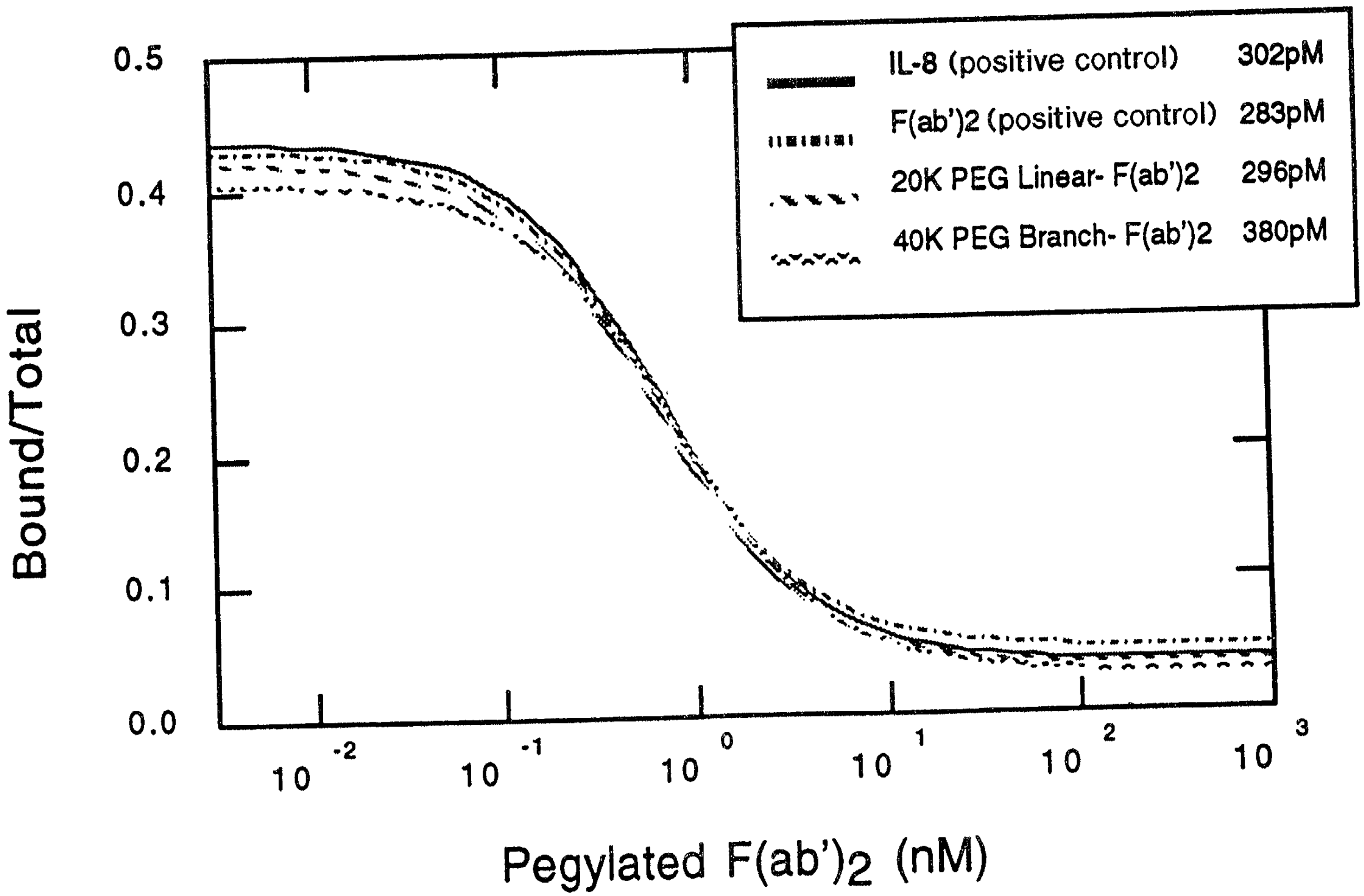

IL-8 (positive control) 302pM
F(ab')2 (positive control) 283pM
20K PEG Linear- F(ab')2 296pM
40K PEG Branch- F(ab')2 380pM
Bound/Total
0.5
0.4
0.3
0.2
0.1
0.0
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
10^{3}
Pegylated F(ab')$_2$ (nM)

FIG. 57A

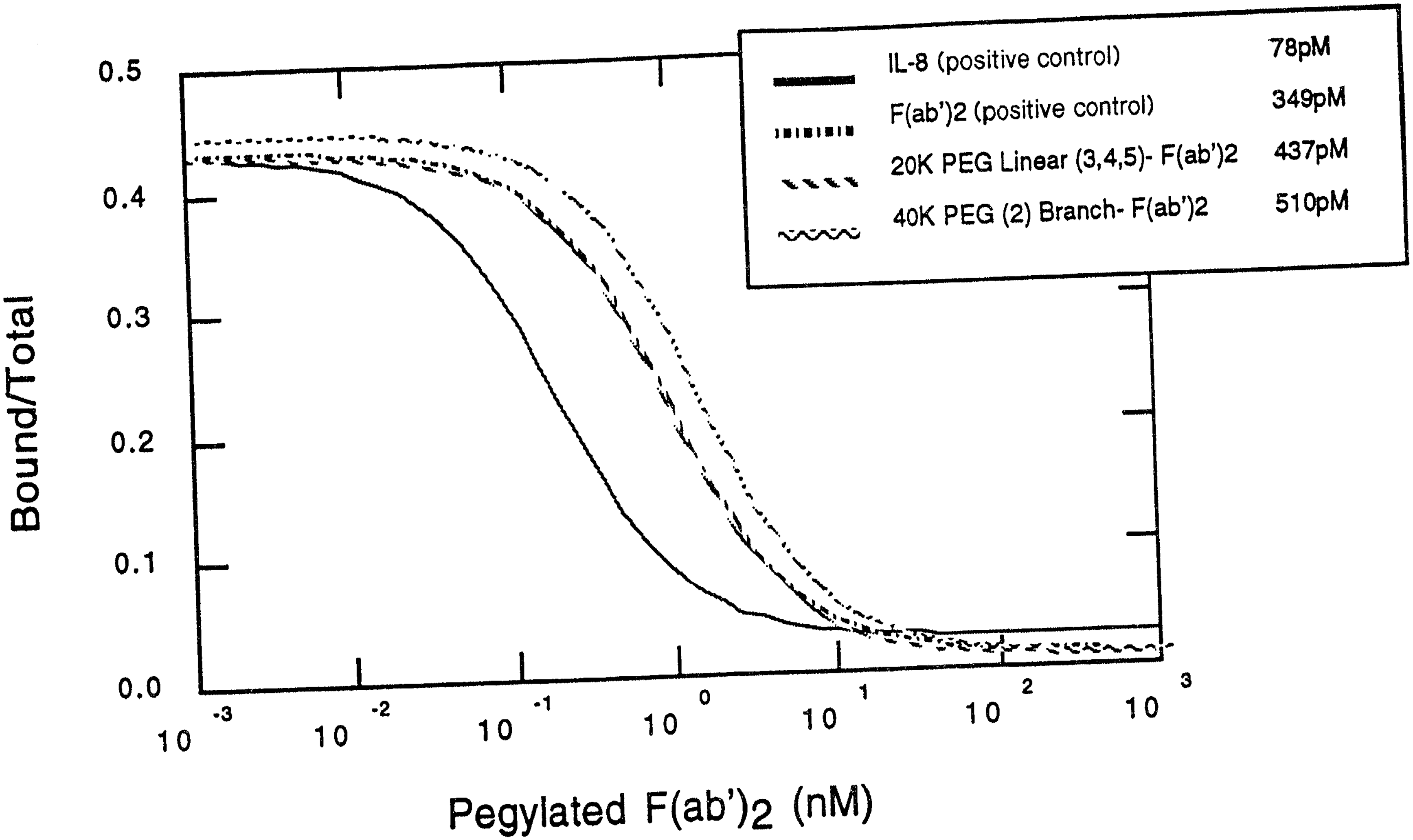

IL-8 (positive control) 78pM
F(ab')2 (positive control) 349pM
20K PEG Linear (3,4,5)- F(ab')2 437pM
40K PEG (2) Branch- F(ab')2 510pM
Bound/Total
0.5
0.4
0.3
0.2
0.1
0.0
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
10^{3}
Pegylated $F(ab')_2$ (nM)

FIG. 57B

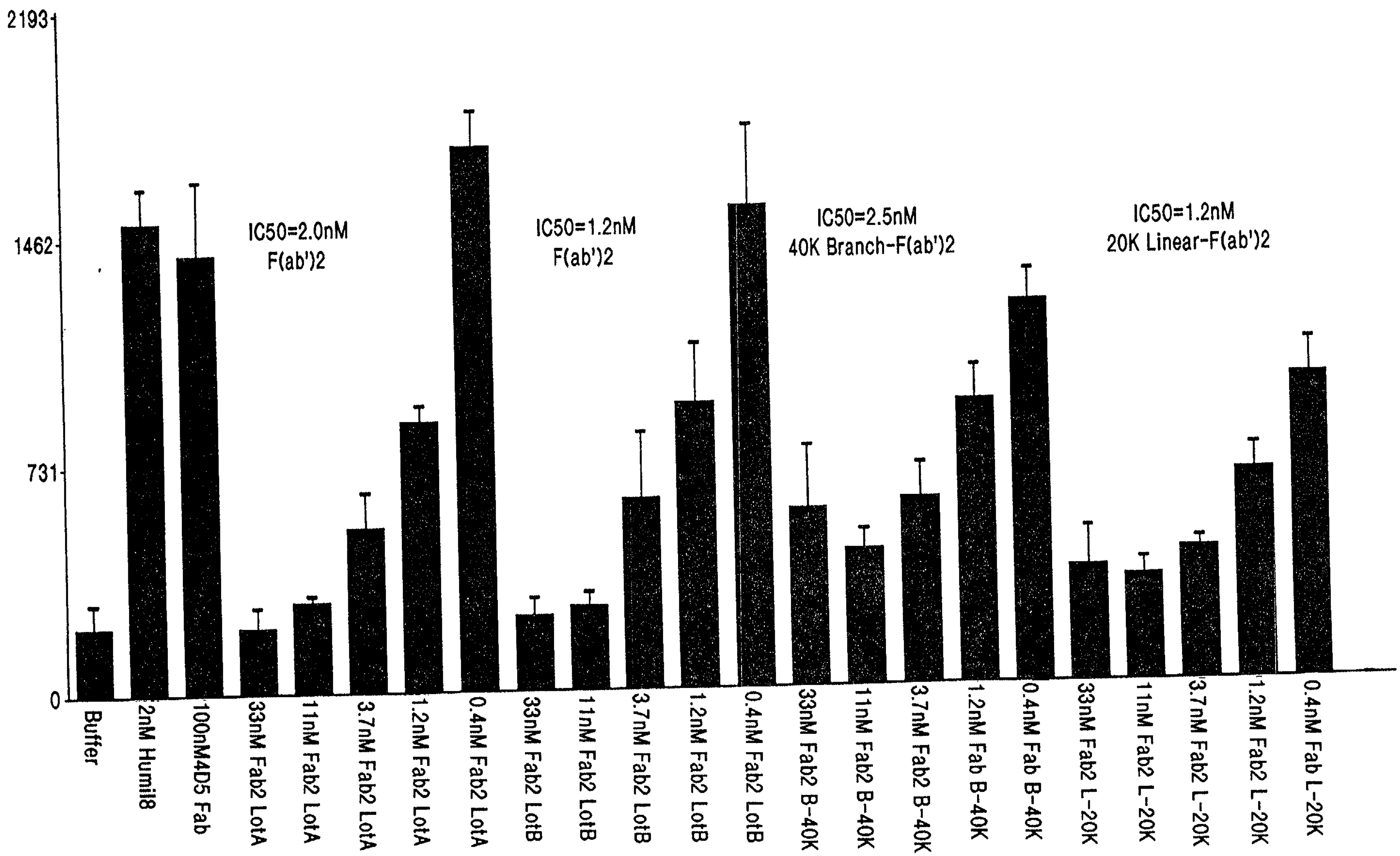
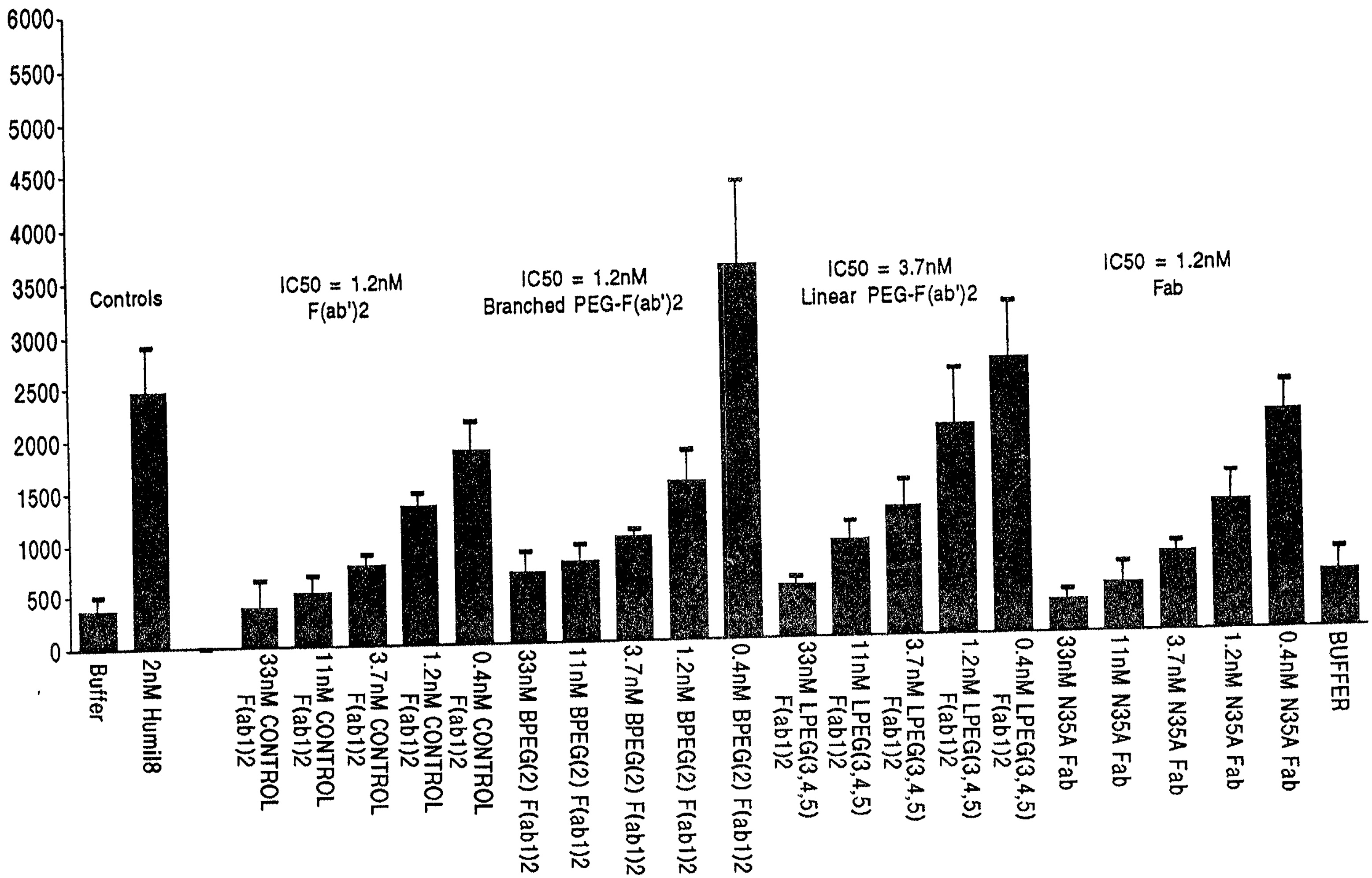
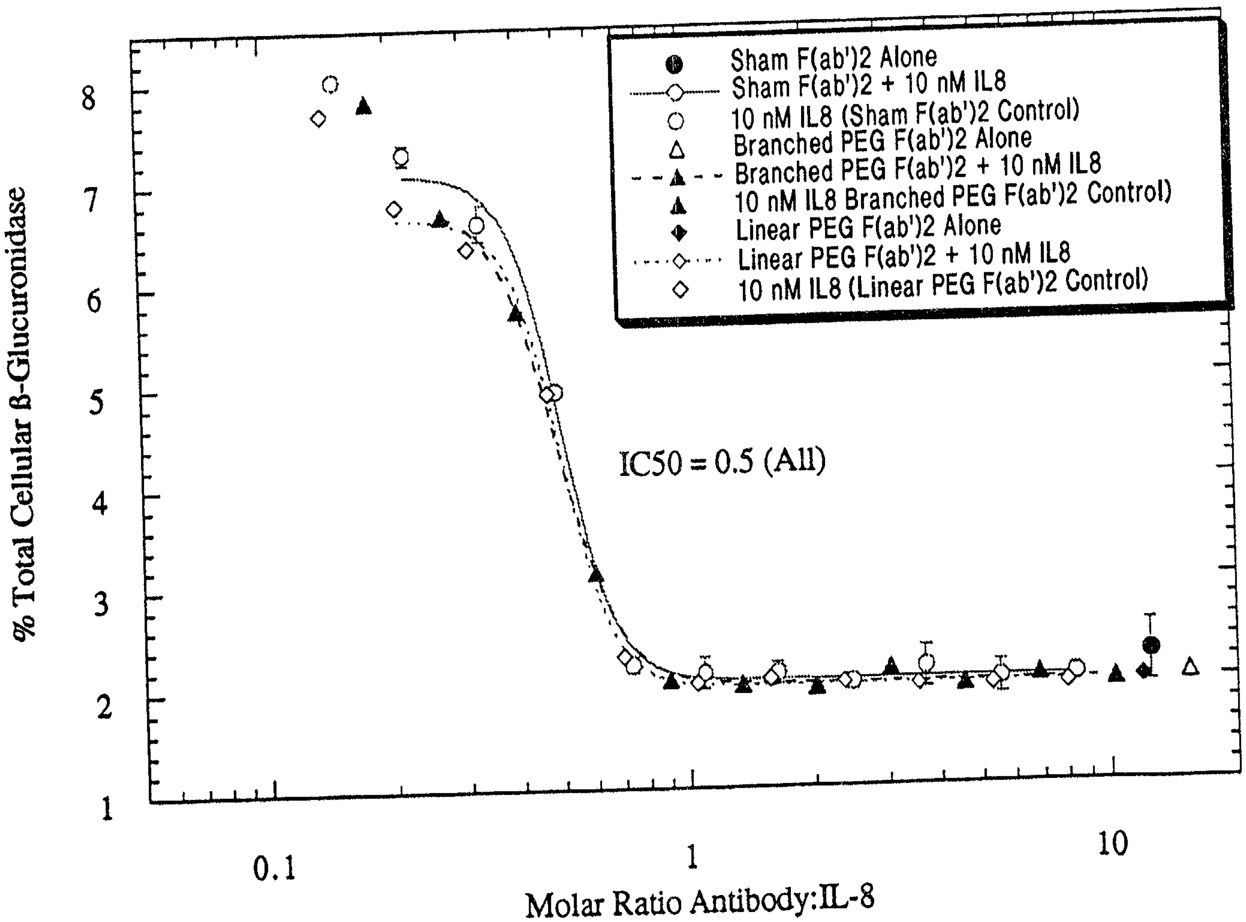

2193
1462
731
0
IC50=2.0nM
F(ab')2
IC50=1.2nM
F(ab')2
IC50=2.5nM
40K Branch-F(ab')2
IC50=1.2nM
20K Linear-F(ab')2
Buffer
2nM Humil8
100nM4D5 Fab
33nM Fab2 LotA
11nM Fab2 LotA
3.7nM Fab2 LotA
1.2nM Fab2 LotA
0.4nM Fab2 LotA
33nM Fab2 LotB
11nM Fab2 LotB
3.7nM Fab2 LotB
1.2nM Fab2 LotB
0.4nM Fab2 LotB
33nM Fab2 B-40K
11nM Fab2 B-40K
3.7nM Fab2 B-40K
1.2nM Fab B-40K
0.4nM Fab B-40K
33nM Fab2 L-20K
11nM Fab2 L-20K
3.7nM Fab2 L-20K
1.2nM Fab2 L-20K
0.4nM Fab L-20K

FIG. 58A



6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
Controls
IC50 = 1.2nM F(ab')2
IC50 = 1.2nM Branched PEG-F(ab')2
IC50 = 3.7nM Linear PEG-F(ab')2
IC50 = 1.2nM Fab
Buffer
2nM Humil8
33nM CONTROL F(ab1)2
11nM CONTROL F(ab1)2
3.7nM CONTROL F(ab1)2
1.2nM CONTROL F(ab1)2
0.4nM CONTROL F(ab1)2
33nM BPEG(2) F(ab1)2
11nM BPEG(2) F(ab1)2
3.7nM BPEG(2) F(ab1)2
1.2nM BPEG(2) F(ab1)2
0.4nM BPEG(2) F(ab1)2
33nM LPEG(3,4,5) F(ab1)2
11nM LPEG(3,4,5) F(ab1)2
3.7nM LPEG(3,4,5) F(ab1)2
1.2nM LPEG(3,4,5) F(ab1)2
0.4nM LPEG(3,4,5) F(ab1)2
33nM N35A Fab
11nM N35A Fab
3.7nM N35A Fab
1.2nM N35A Fab
0.4nM N35A Fab
BUFFER

FIG. 58B



Sham F(ab')2 Alone
Sham F(ab')2 + 10 nM IL8
10 nM IL8 (Sham F(ab')2 Control)
Branched PEG F(ab')2 Alone
Branched PEG F(ab')2 + 10 nM IL8
10 nM IL8 Branched PEG F(ab')2 Control)
Linear PEG F(ab')2 Alone
Linear PEG F(ab')2 + 10 nM IL8
10 nM IL8 (Linear PEG F(ab')2 Control)
IC50 = 0.5 (All)
% Total Cellular ß-Glucuronidase
8
7
6
5
4
3
2
1
0.1
1
10
Molar Ratio Antibody:IL-8

FIG. 59A

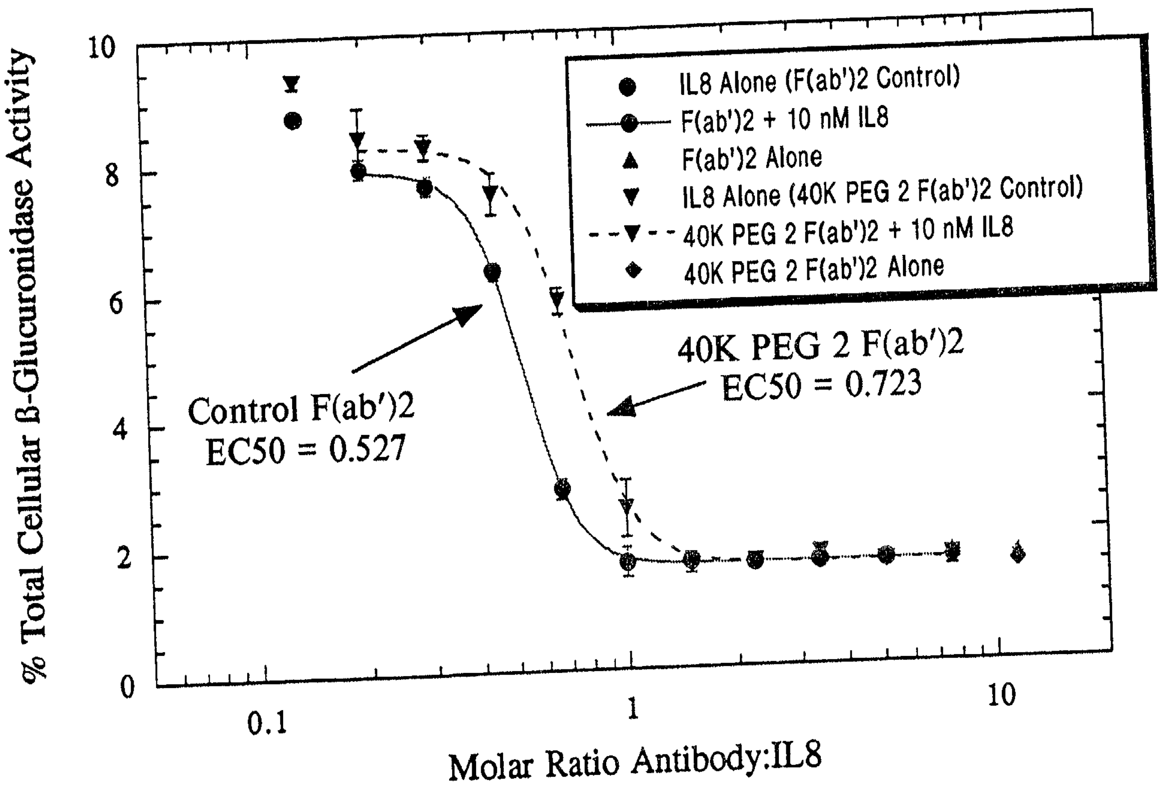

IL8 Alone (F(ab')2 Control)
F(ab')2 + 10 nM IL8
F(ab')2 Alone
IL8 Alone (40K PEG 2 F(ab')2 Control)
40K PEG 2 F(ab')2 + 10 nM IL8
40K PEG 2 F(ab')2 Alone
Control F(ab')2
EC50 = 0.527
40K PEG 2 F(ab')2
EC50 = 0.723
% Total Cellular ß-Glucuronidase Activity
Molar Ratio Antibody:IL8
0
2
4
6
8
10
0.1
1
10

FIG. 59B

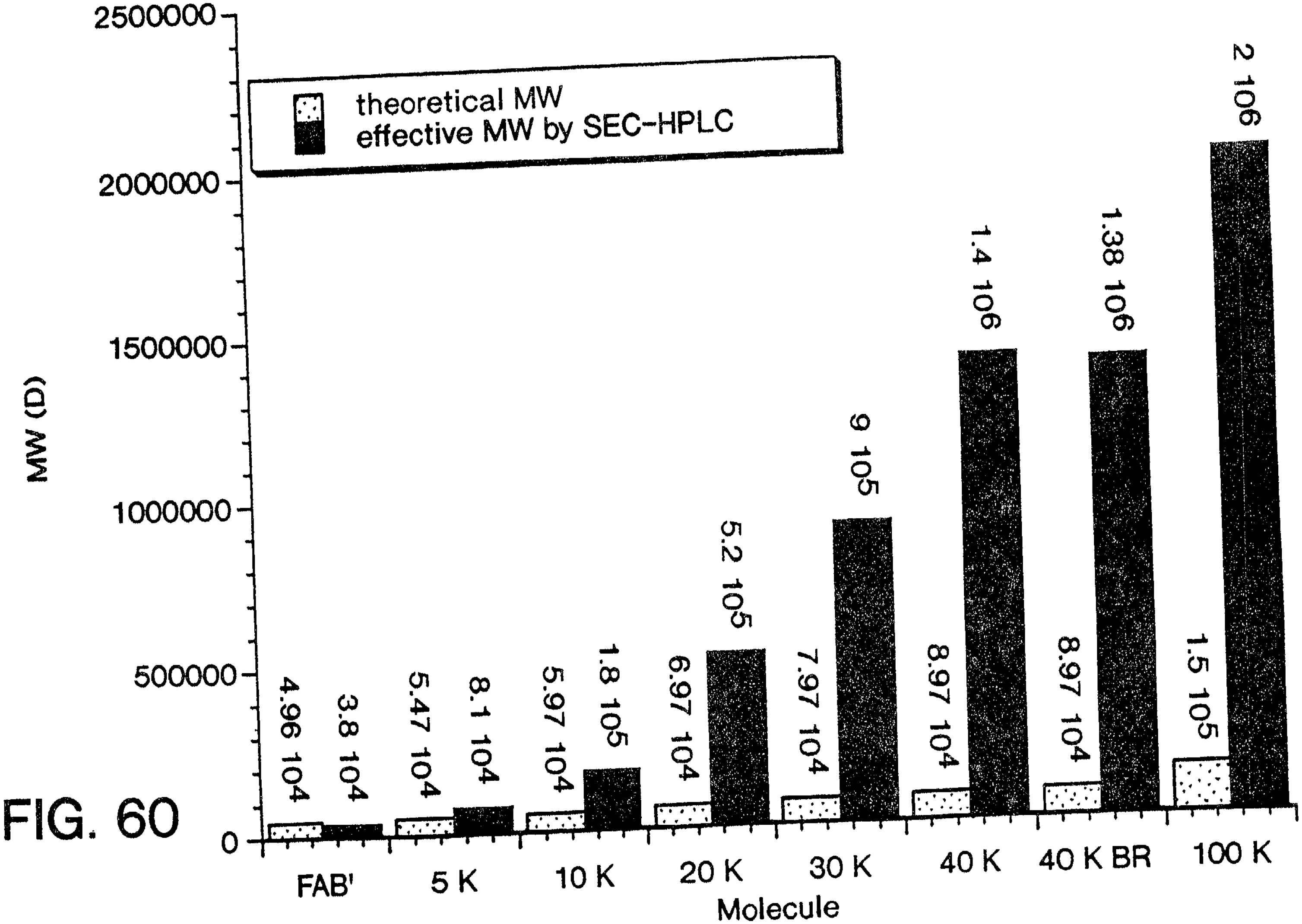

theoretical MW
effective MW by SEC-HPLC
MW (D)
2500000
2000000
1500000
1000000
500000
0
4.96 10^4
3.8 10^4
5.47 10^4
8.1 10^4
5.97 10^4
1.8 10^5
6.97 10^4
5.2 10^5
7.97 10^4
9 10^5
8.97 10^4
1.4 10^6
8.97 10^4
1.38 10^6
1.5 10^5
2 10^6
FAB'
5 K
10 K
20 K
30 K
40 K
40 K BR
100 K
Molecule

FIG. 60

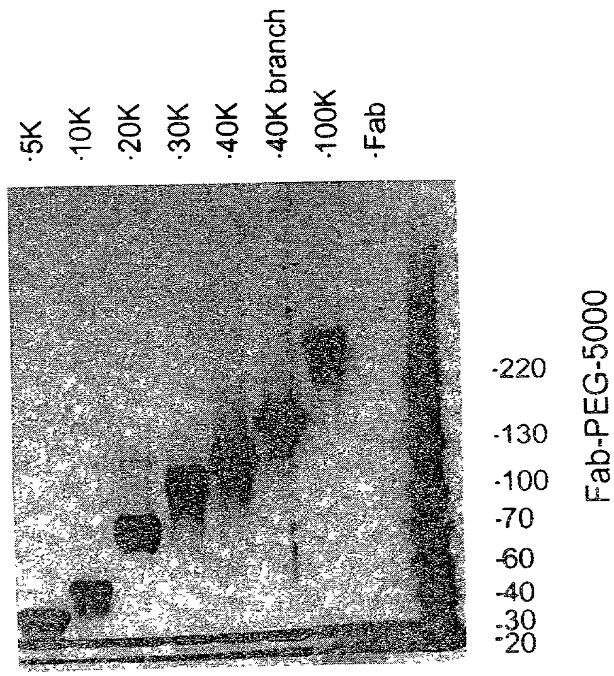


FIG. 61A

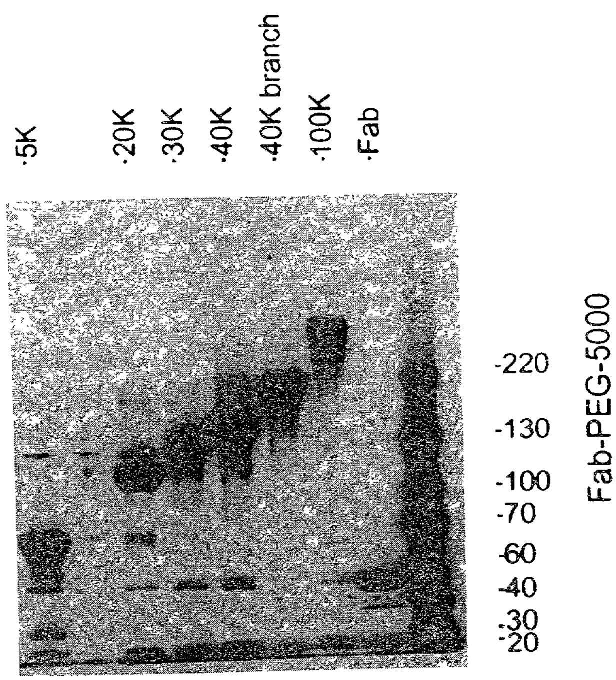
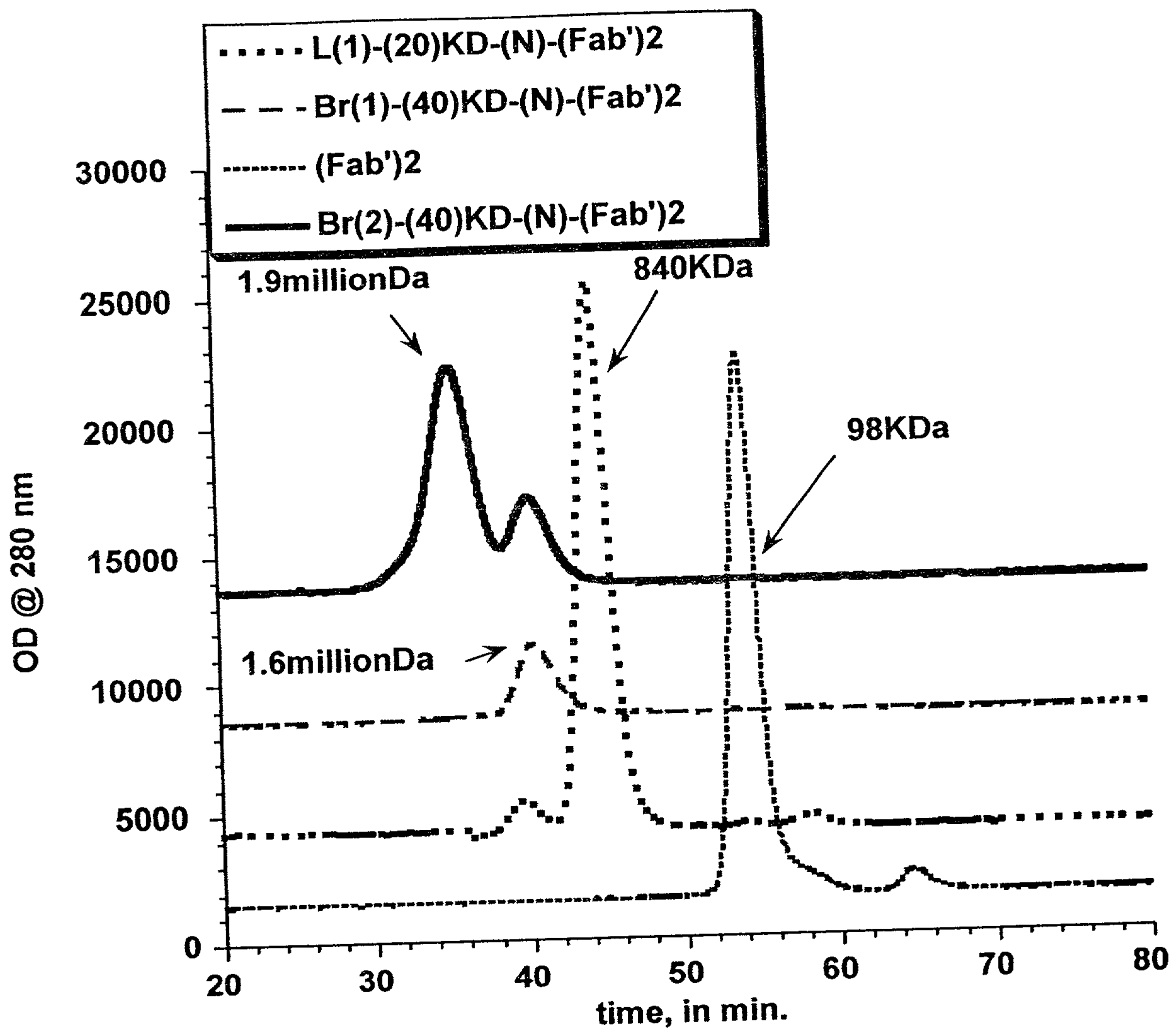


FIG. 61B



L(1)-(20)KD-(N)-(Fab')2
Br(1)-(40)KD-(N)-(Fab')2
(Fab')2
Br(2)-(40)KD-(N)-(Fab')2
1.9millionDa
840KDa
98KDa
1.6millionDa
OD @ 280 nm
30000
25000
20000
15000
10000
5000
0
20
30
40
50
60
70
80
time, in min.

FIG. 62

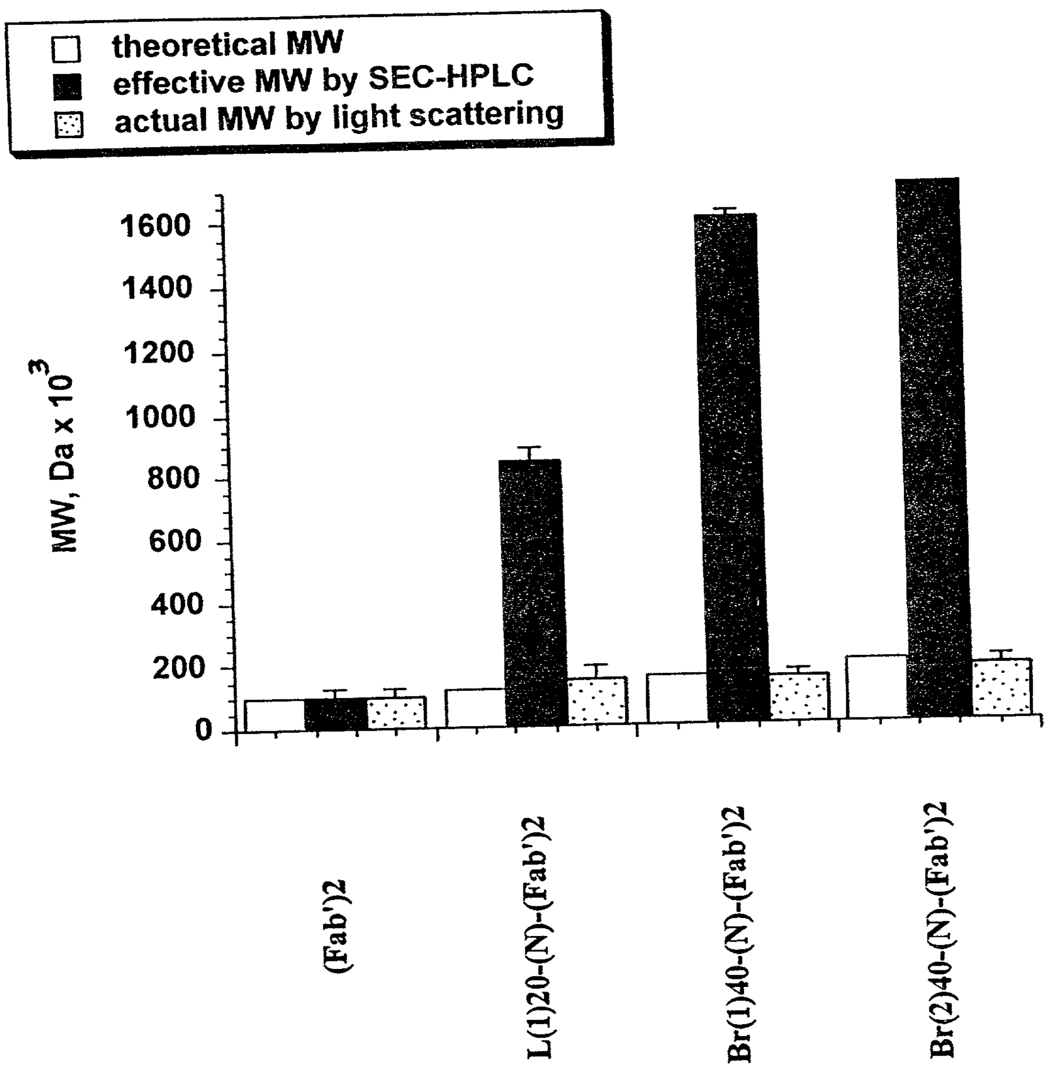

theoretical MW
effective MW by SEC-HPLC
actual MW by light scattering
MW, Da x 10^3
1600
1400
1200
1000
800
600
400
200
0
(Fab')2
L(1)20-(N)-(Fab')2
Br(1)40-(N)-(Fab')2
Br(2)40-(N)-(Fab')2

FIG. 63

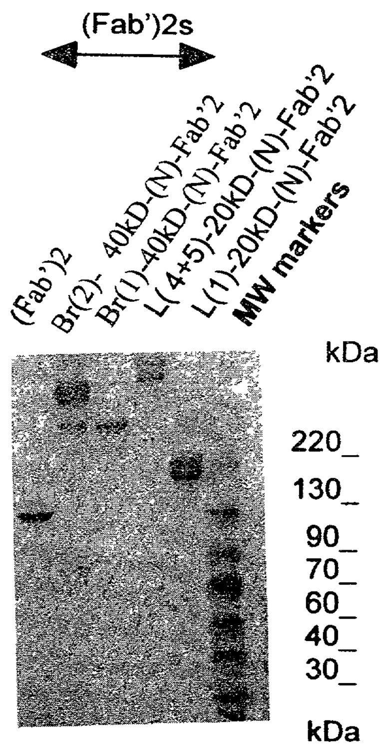

(Fab')2s
(Fab')2
Br(2)- 40kD-(N)-Fab'2
Br(1)-40kD-(N)-Fab'2
L(4+5)-20kD-(N)-Fab'2
L(1)-20kD-(N)-Fab'2
MW markers
kDa
220_
130_
90_
70_
60_
40_
30_
kDa

FIG. 64

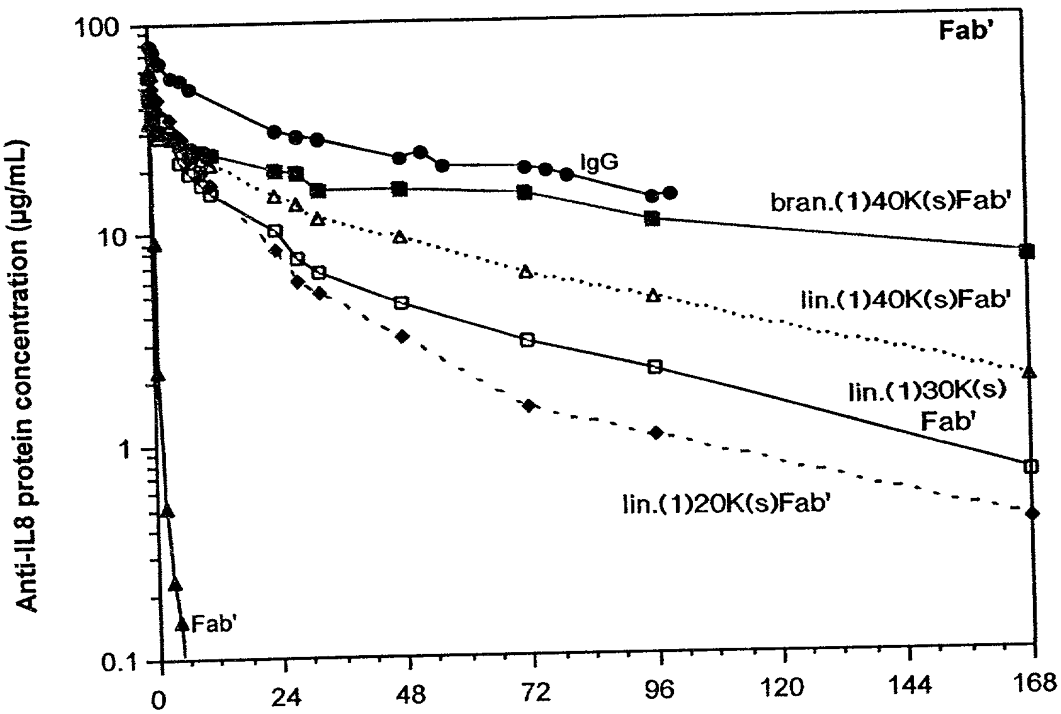


FIG. 65A

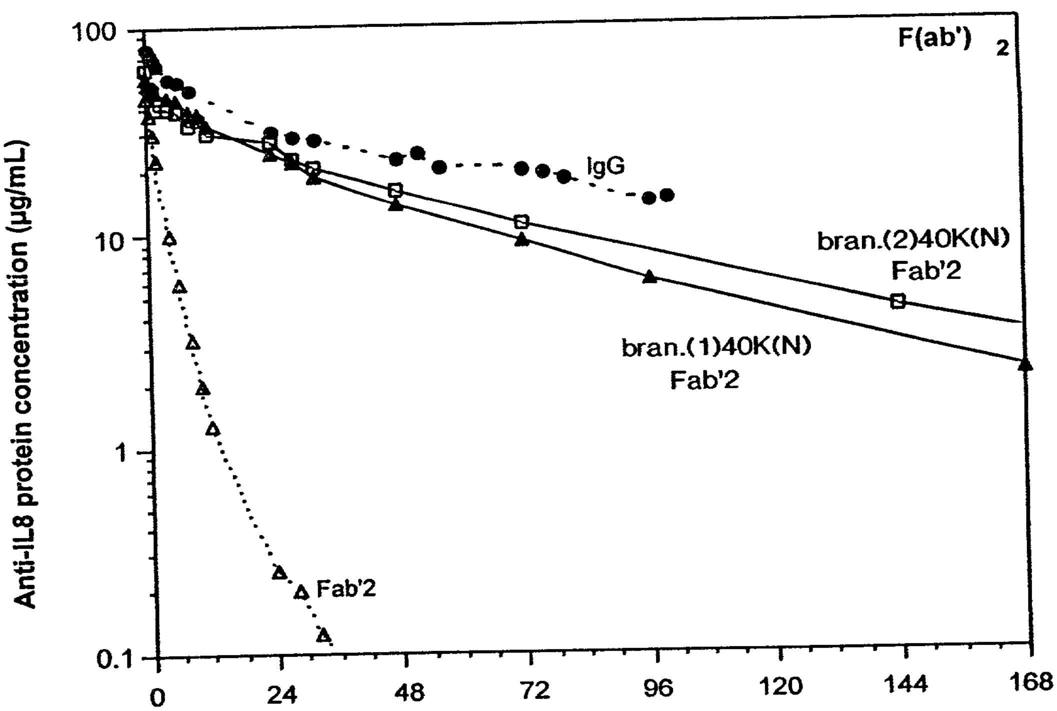
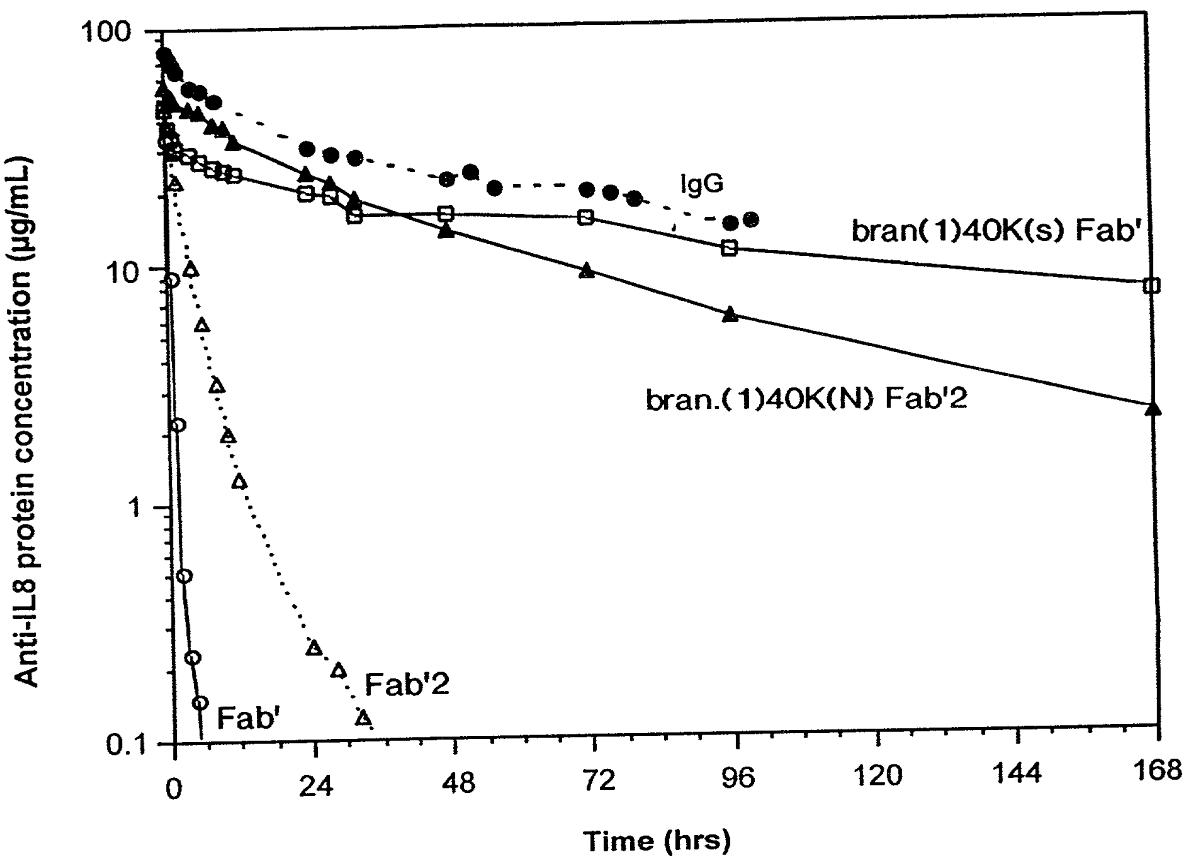
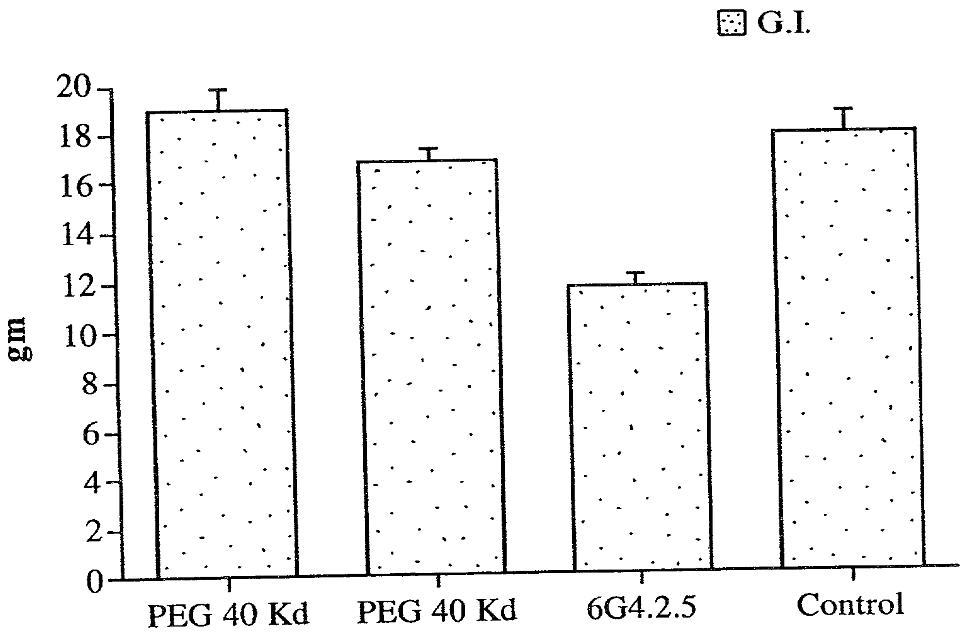


FIG. 65B



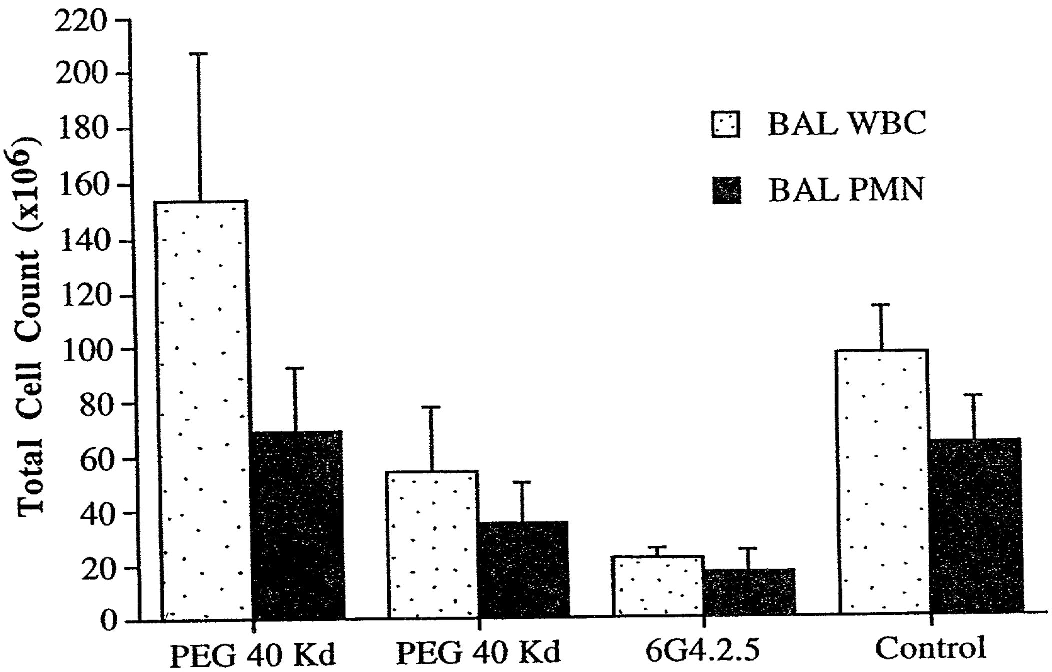
Anti-IL8 protein concentration (µg/mL)
100
10
1
0.1
0
24
48
72
96
120
144
168
Time (hrs)
IgG
bran(1)40K(s) Fab'
bran.(1)40K(N) Fab'2
Fab'2
Fab'

FIG. 66



G.I.
gm
0
2
4
6
8
10
12
14
16
18
20
PEG 40 Kd
PEG 40 Kd
6G4.2.5
Control

FIG. 67



Total Cell Count (x106)
0
20
40
60
80
100
120
140
160
180
200
220
BAL WBC
BAL PMN
PEG 40 Kd
PEG 40 Kd
6G4.2.5
Control

FIG. 68

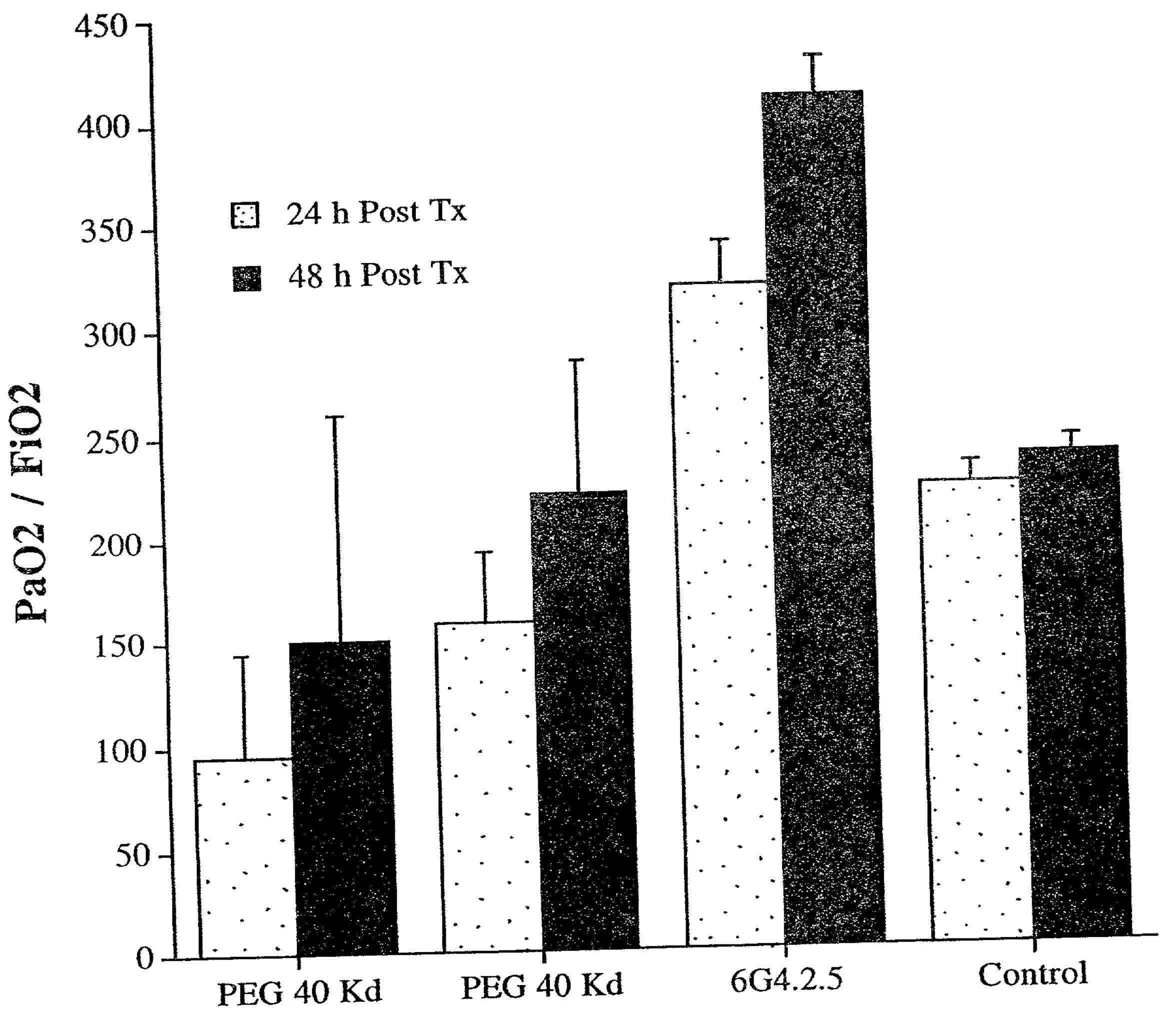

450
400
350
300
250
200
150
100
50
0
PaO2 / FiO2
24 h Post Tx
48 h Post Tx
PEG 40 Kd
PEG 40 Kd
6G4.2.5
Control

FIG. 69

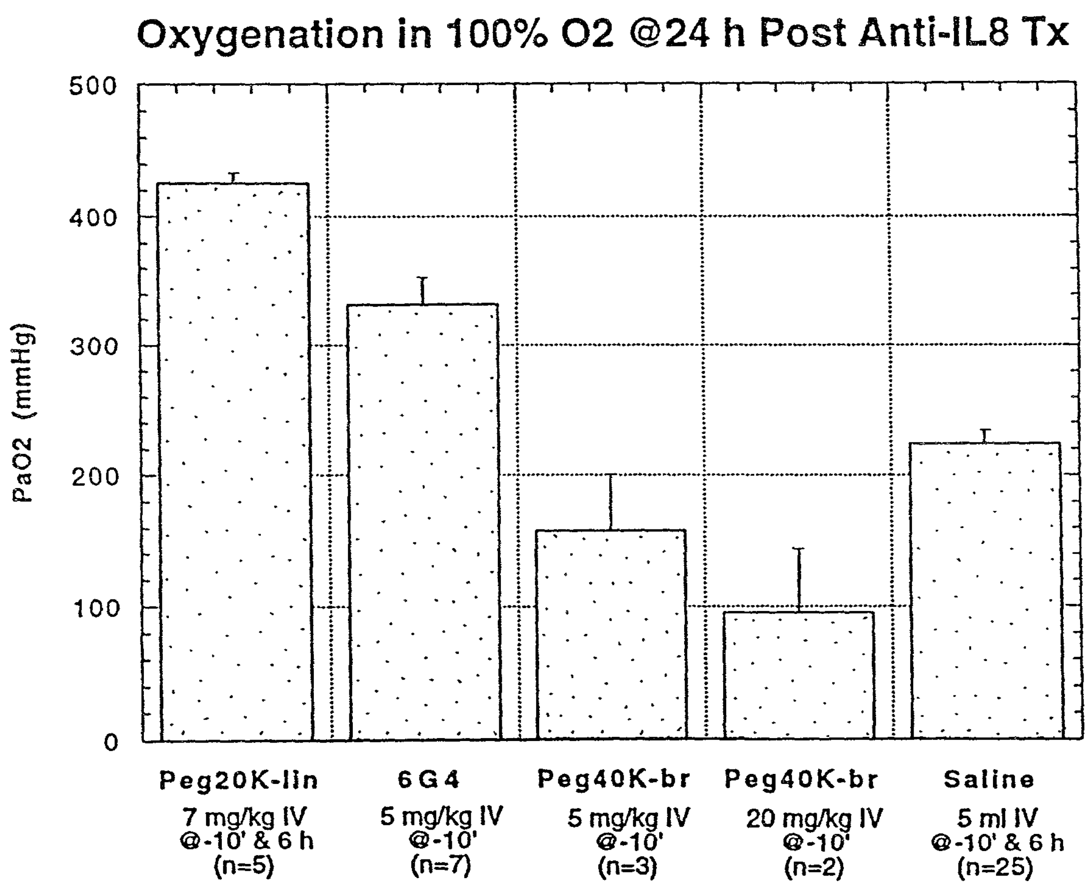
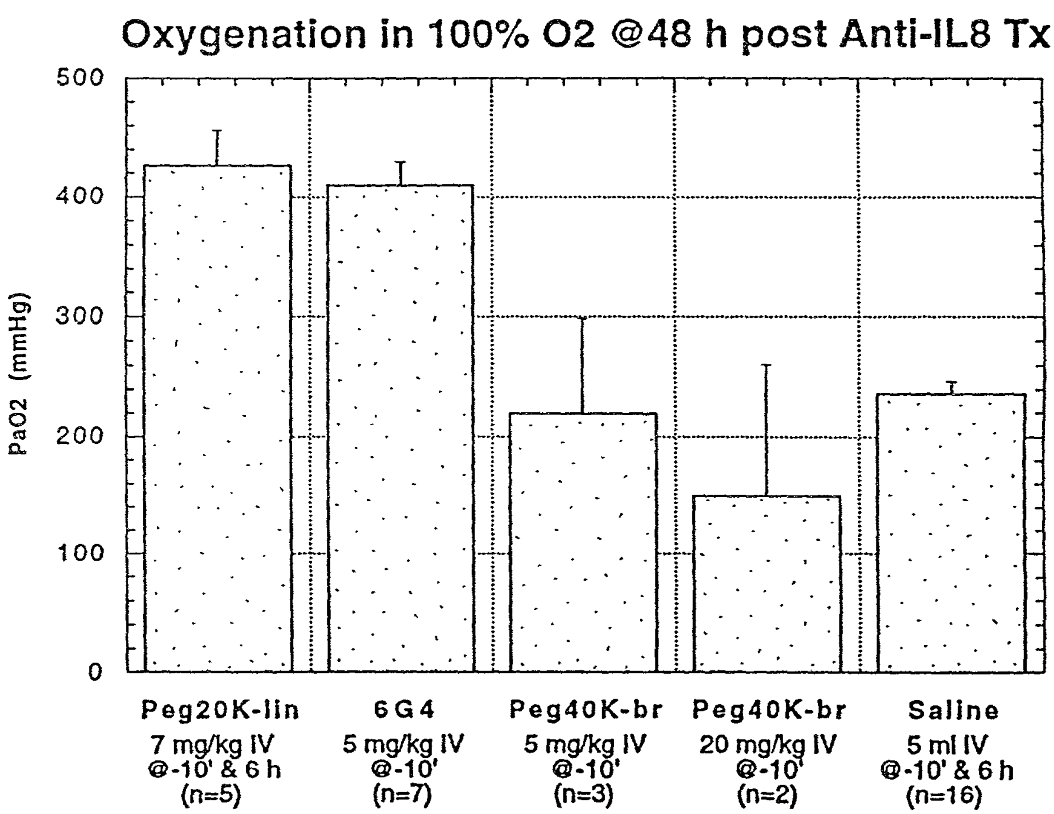

Oxygenation in 100% O2 @24 h Post Anti-IL8 Tx
PaO2 (mmHg)
500
400
300
200
100
0
Peg20K-lin
7 mg/kg IV
@-10' & 6 h
(n=5)
6G4
5 mg/kg IV
@-10'
(n=7)
Peg40K-br
5 mg/kg IV
@-10'
(n=3)
Peg40K-br
20 mg/kg IV
@-10'
(n=2)
Saline
5 ml IV
@-10' & 6 h
(n=25)

FIG. 70A



Oxygenation in 100% O2 @48 h post Anti-IL8 Tx
PaO2 (mmHg)
500
400
300
200
100
0
Peg20K-lin
7 mg/kg IV
@-10' & 6 h
(n=5)
6G4
5 mg/kg IV
@-10'
(n=7)
Peg40K-br
5 mg/kg IV
@-10'
(n=3)
Peg40K-br
20 mg/kg IV
@-10'
(n=2)
Saline
5 ml IV
@-10' & 6 h
(n=16)

FIG. 70B

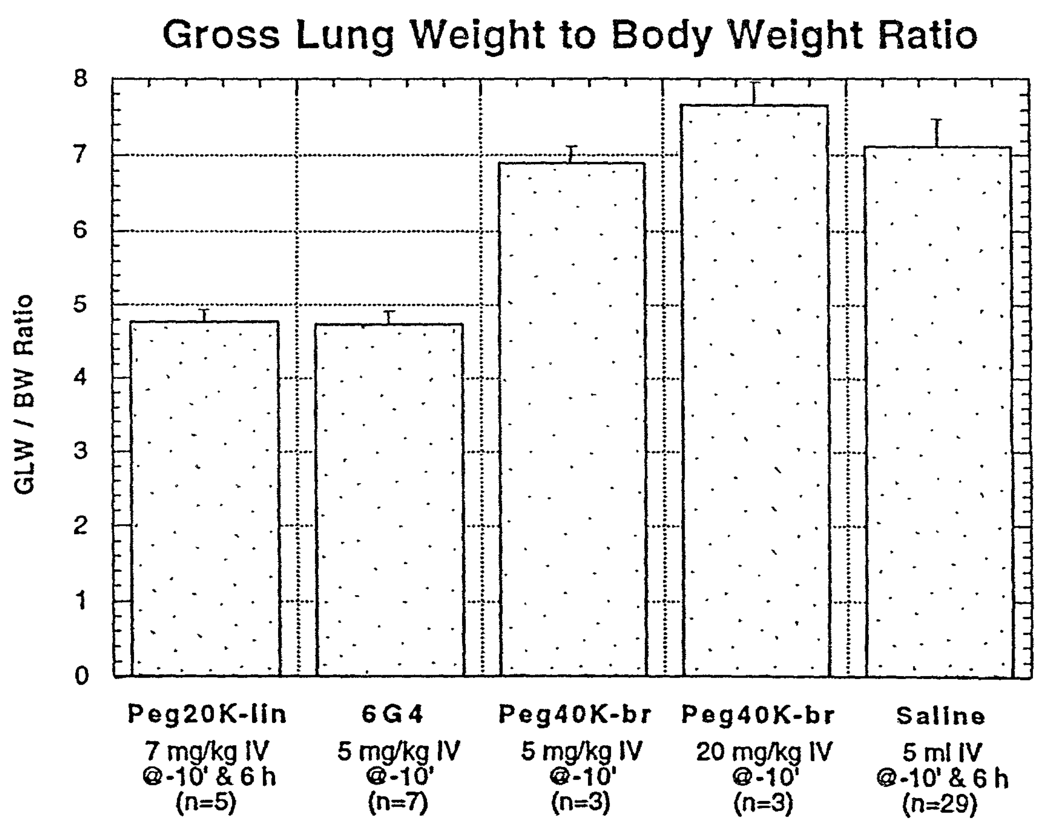

Gross Lung Weight to Body Weight Ratio
GLW / BW Ratio
0
1
2
3
4
5
6
7
8
Peg20K-lin
7 mg/kg IV
@-10' & 6 h
(n=5)
6G4
5 mg/kg IV
@-10'
(n=7)
Peg40K-br
5 mg/kg IV
@-10'
(n=3)
Peg40K-br
20 mg/kg IV
@-10'
(n=3)
Saline
5 ml IV
@-10' & 6 h
(n=29)

FIG. 70C

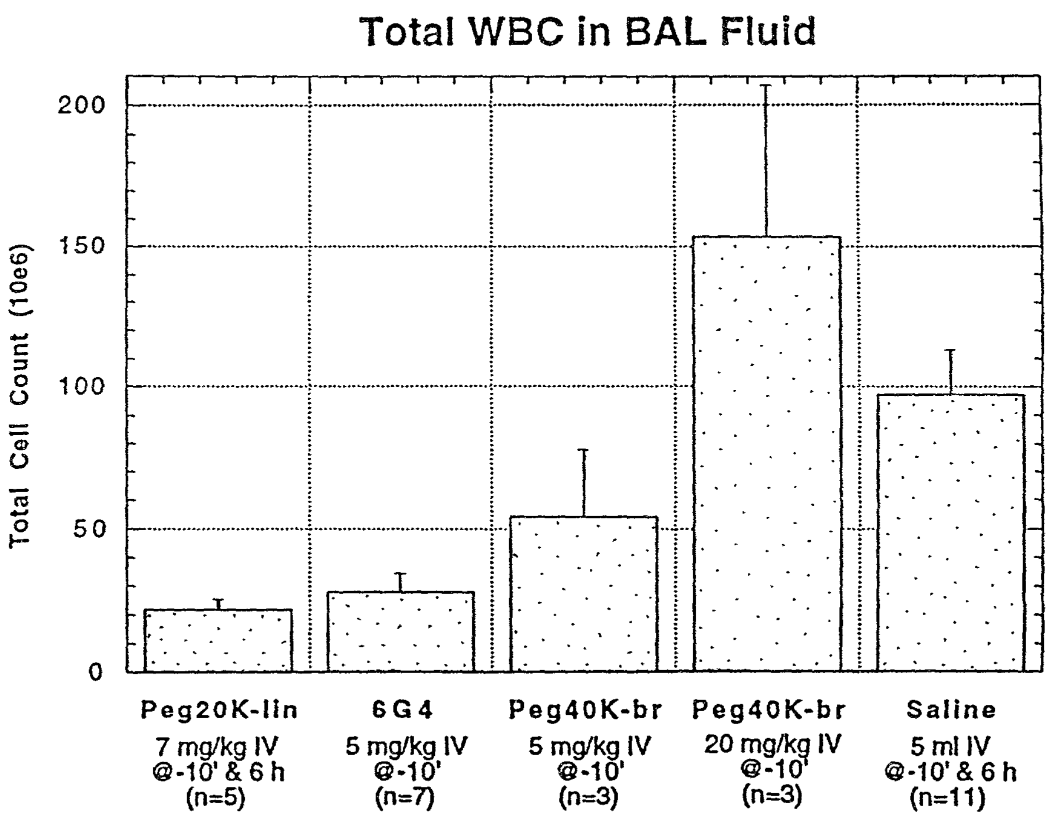

Total WBC in BAL Fluid
Total Cell Count (10e6)
200
150
100
50
0
Peg20K-lin
7 mg/kg IV
@-10' & 6 h
(n=5)
6G4
5 mg/kg IV
@-10'
(n=7)
Peg40K-br
5 mg/kg IV
@-10'
(n=3)
Peg40K-br
20 mg/kg IV
@-10'
(n=3)
Saline
5 ml IV
@-10' & 6 h
(n=11)

FIG. 70D

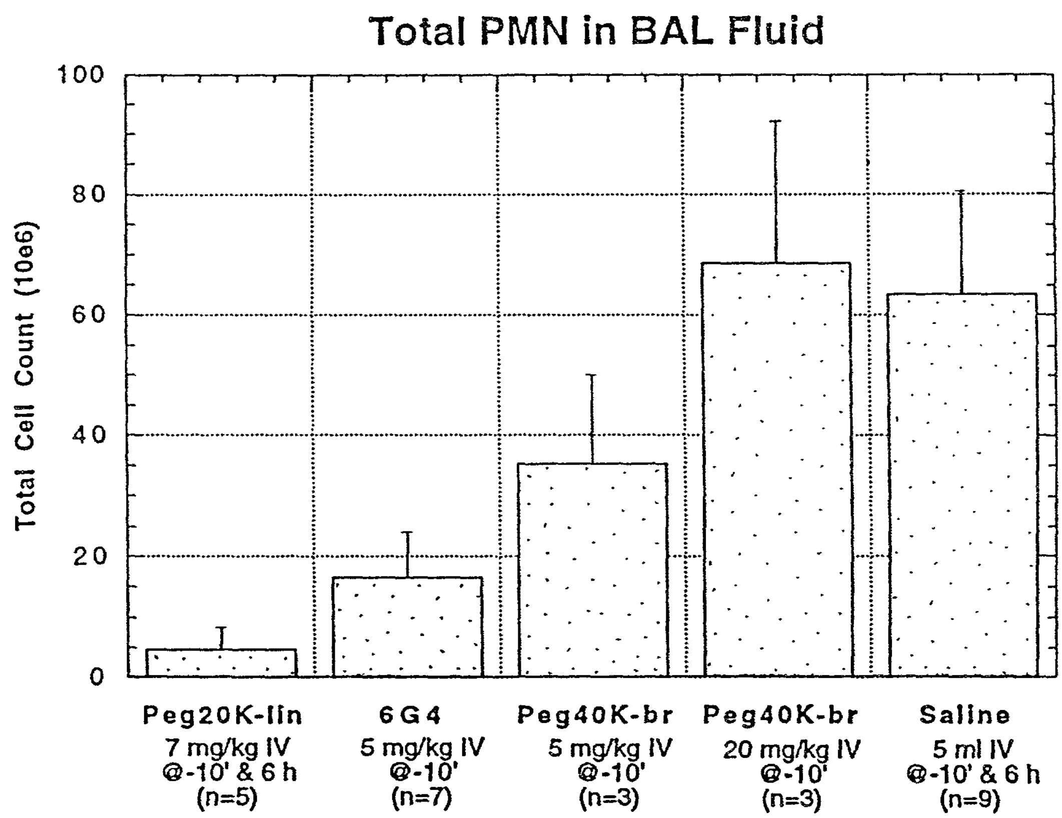
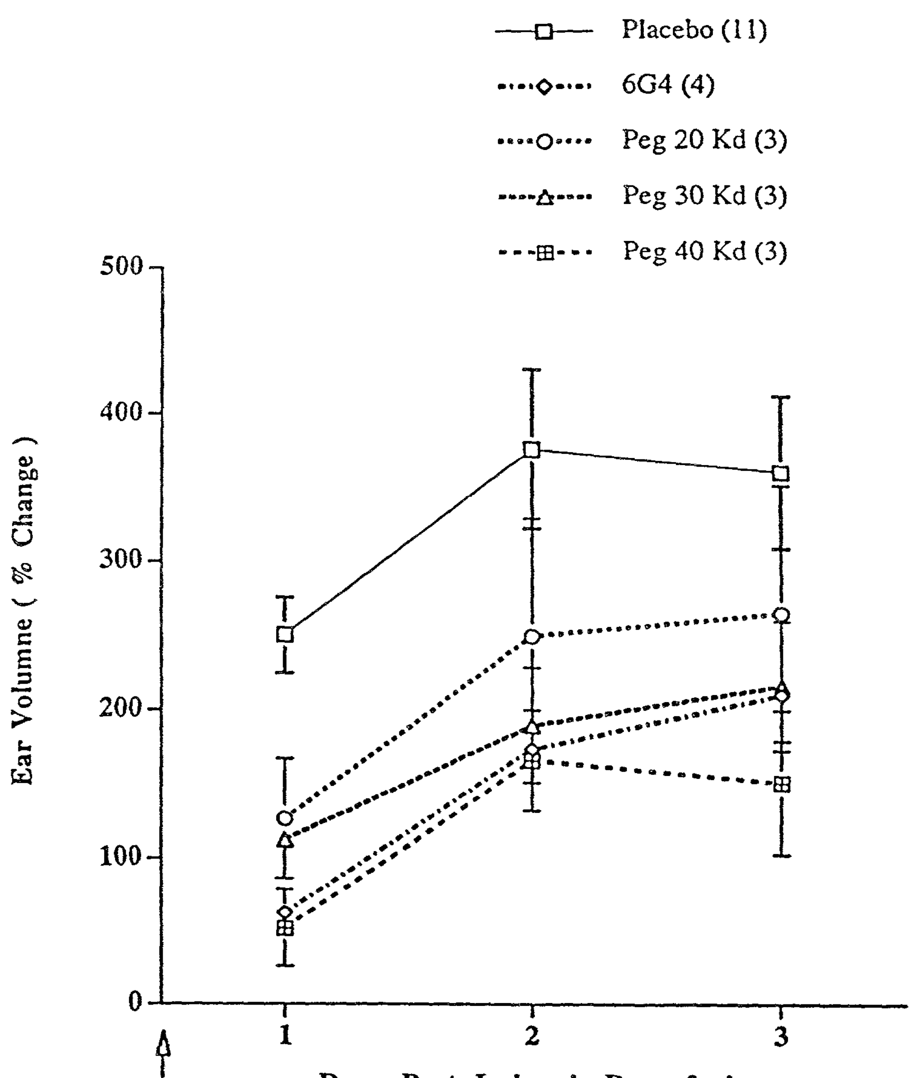

Total PMN in BAL Fluid
Total Cell Count (10e6)
0
20
40
60
80
100
Peg20K-lin
7 mg/kg IV
@-10' & 6 h
(n=5)
6G4
5 mg/kg IV
@-10'
(n=7)
Peg40K-br
5 mg/kg IV
@-10'
(n=3)
Peg40K-br
20 mg/kg IV
@-10'
(n=3)
Saline
5 ml IV
@-10' & 6 h
(n=9)

FIG. 70E

The Effect of Pegylated Anti-IL-8 in the Rabbit Ear model of Ischemia-Reperfusion Injury



Anti-IL-8 formulations :
Single Dose (5 mg/kg)
administered IV at time
of reperfusion

FIG. 71